LES CONCEPTS

DE

CLAUDE BERNARD

SUR LE

MILIEU INTÉRIEUR

par

ROGER HEIM, BERNARD HALPERN, YVON BOURGES, BENGT ANDERSSON,
OTTO H. GAUER, ROBERT F. PITTS, JAMES F. DANIELLI, FRANÇOIS MOREL,
CORNEILLE HEYMANS, ERIC NEIL, OSCAR M. HELMER, IRVINE H. PAGE,
JAMES W. McCURBIN, PHILIPPE MEYER, C. CHEVILLARD, PAUL MILLIEZ,
BJÖRN FOLKOW, LYSLE H. PETERSON, E. WITZLEB, MAGNUS I. GREGERSEN,
JAMES D. HARDY, CHARLES KAYSER, T. H. BENZINGER, LAURENCE IRVING,
J. CHATONNET, ALBERT SZENT·GYORGYI
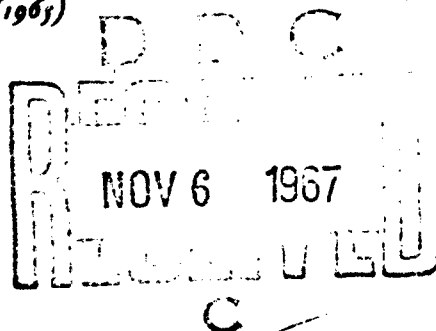
THE THERMAL HOMEOSTASIS
OF MAN [1]

by

T. H. BENZINGER

(Bio-Energetics Laboratories, Naval Medical Research Institute,
Bethesda, Maryland [U. S. A.]).

INTRODUCTION

In warm-blooded animals and man, homeostasis of internal temperature is maintained against wide variations of thermal flux from external or internal sources. The thermal *milieu intérieur* is closely guarded. Gains of heat (in warmth) are answered by equivalent physiological losses. Forced losses of heat (in cold) are balanced by equivalent internal gains. The principal effector mechanisms of thermoregulation, evaporative loss of heat by sweating and metabolic gain of heat by food combustion, were recognized in the early history of modern science, by Antoine Lavoisier and by Benjamin Franklin.

It was Claude Bernard who first described a third kind of thermoregulatory response : Vascmotor action. It was he who envisioned supreme control of the central nervous system over all thermoregulatory activities. The most important contribution to future research on thermal homeostasis, however, was Claude Bernard's concept of absolute determinism in experimental medicine. He rejected the idea of a vital force, or spontaneity in living matter. He refused to surrender before the complexity of multiple factors in phenomena of life. It was his belief, that when the conditions of the experiment are kept identical, a phenomenon will never fail to produce itself in the same manner, no matter how complex the situation as a whole may be. Applied to the thermal homeostasis of man, determinism of experimental medicine leads to a major challenge : to find amongst the great variety of thermal phenomena in the body those factors which cause in a

reproducible and quantitative manner, the astonishing phenomenon of near-invariance of internal temperature.

Homeostasis of internal temperature cannot be closely maintained unless small deviations from the norm elicit substantial responses in loss or gain of heat. These must be related in a reproducible and quantitative manner to thermal stimuli by which they are caused when stimuli impinge upon receptive structures. New methods of measurement have permitted to find such reproducible stimulus-response relations. They were observed only in
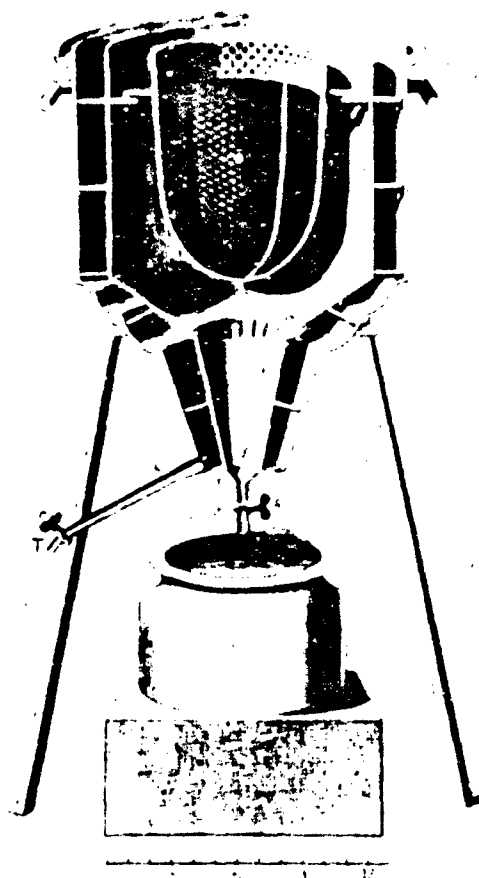

Fig. 1.

The Animal Calorimeter of Antoine Lavoisier [1] *measured the rate of heat loss by the rate of melting of ice.*

more advanced phases, not in the early stages of our work. Initial failures and their reasons shall be reported as well as the eventual results.

Physiological mechanisms depend on anatomical structures. During the century following Claude Bernard's *Introduction to the Study of Experimental Medicine,* an anatomical basis for neural stimuli and responses in thermoregulation has been provided through a sequence of outstanding discoveries. These include : 1° a « center » indispensable for « physical » temperature regulation, proven to exist by Richet, and found to be located in the anterior hypothalamus by Aronsohn and Sachs (1884-1885); 2° sensitivity of this anterior hypothalamic « heat loss center » to temperature, discovered by Barbour (1912); 3° a second « center », indispensable for « chemical »

temperature regulation, discovered in the posterior hypothalamus by Isenschmidt and Krehl (1912); 4° insensitivity of the posterior hypothalamic « heat maintenance center » to temperature, discovered by Hemingway (1940); 5° thermoreceptors in the human skin, which respond to cold-stimulation with increasing firing rates, discovered by Zotterman and Hensel, (1951 and 1960). To these findings frequent references will be made.

Thermal homeostasis cannot be truly understood without the measurement of temperatures and heat flowrates.
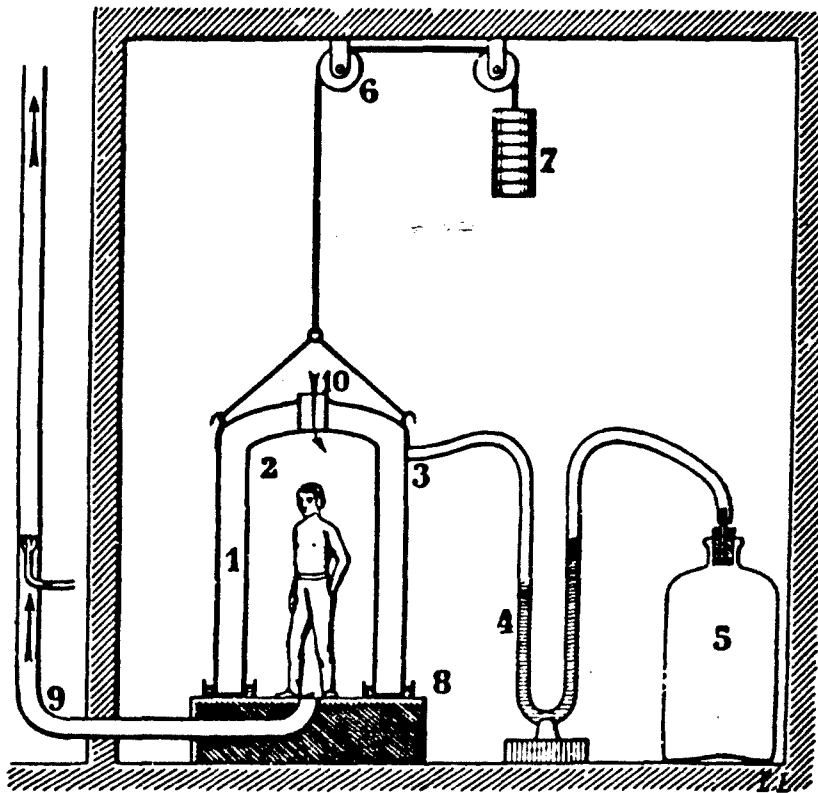

Fig. 2. — *The Human Calorimeter of Arsène d'Arsonval* [2] *measured the rate of heat loss as an increase of temperature and thereby, air pressure, between the double walls of the enclosure.* The surrounding room temperature was kept constant. Errors from changes of barometric pressure were avoided by closing the system with a tank.

While crucial anatomical information on centers and pathways of thermoregulation is obtained on animals with the methods of experimental neurosurgery, only calorimetry permits with animals or man the measurement of total loss or gain of heat, the result of the physiological responses. The art of animal calorimetry originated with Antoine Lavoisier ([1]) (fig. 1).

Outstanding early contributions have been made by Arsène d'Arsonval ([2]) (fig. 2). Together with the work of Charles Richet concerning thermoregulatory responses ([3, 4]) and the role of the central nervous system ([5]) the school of Claude Bernard and French physiology have left their mark forever on the pages of the investigative history of thermoregulation.

METHODS

Classical methods of human calorimetry were too slow, and not versatile enough to record the rapid thermoregulatory changes of various heat flow-rates. A new approach was therefore taken with the principle of gradient layer calorimetry ([6]) (fig. 3). Speed and precision of the new measurement
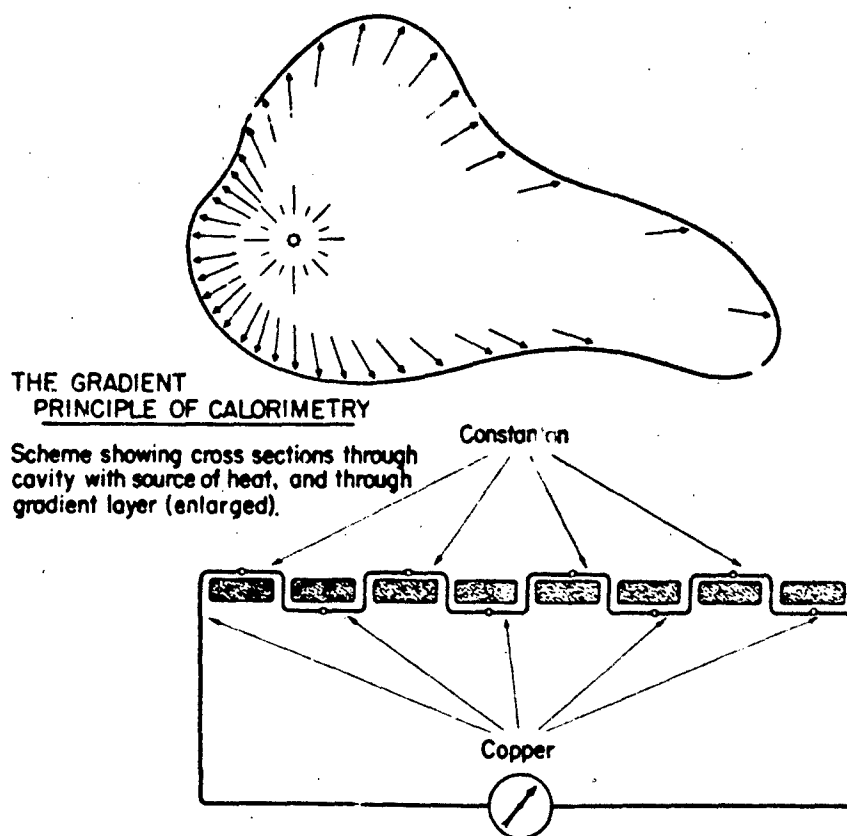

Fig. 3. — *The principle of gradient calorimetry* [8] *permits the integration of total thermal flux in a four pi cavity* (above). Constant temperature is maintained at the walls of the cavity. The walls are lined completely with numerous thin heat-flow-measuring devices of uniform size, distribution and characteristics (below).

were based on the replacement of air-calorimetry [d'Arsonval ([2]), Rubner ([7])] with a solid gradient layer (fig. 4) lining a « four pi cavity » of constant temperature. Complete coverage of this « black body » with a large number of thermoelectric junctions of uniform characteristics and distribution, is an indispensable requirement for precision. Ventilatory and respiratory circuits (fig. 5) provide the partition of radiated, convective and evaporative losses by sweating or respiration. Rapid response and continuous recordings of the human heat loss (fig. 6, *A* and *B*) and its components were first obtained
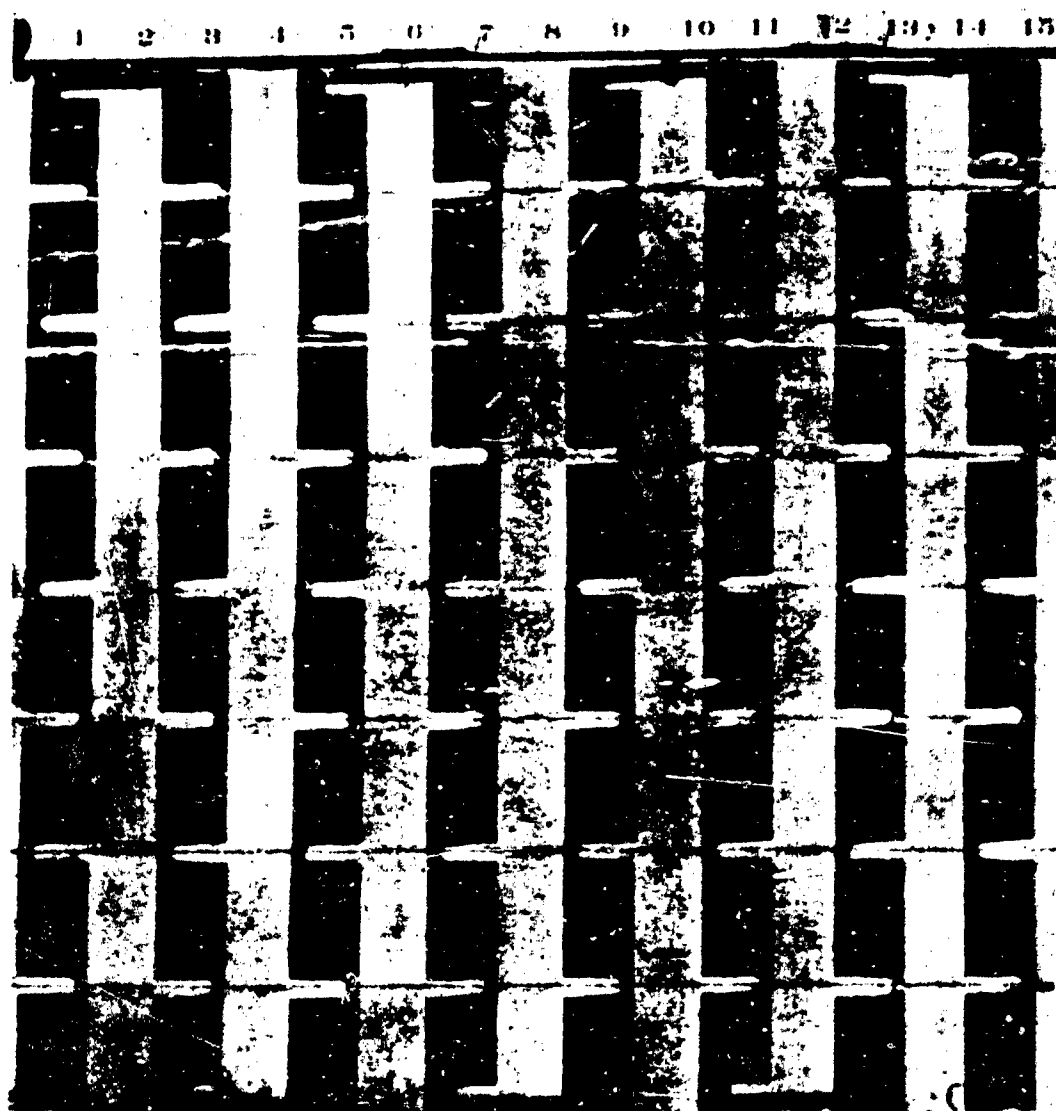
FIG. 4. — A Gradient-layer may be constructed of welded parallel ribbons of copper (dark) and constantan alloy (light). The alternating incisions produce a continuous, alternating sequence of constantan-copper and copper-constantan junctions. The former are located above, the latter underneath a layer of translucent plastic of one millimeter thickness. The electric potential from the two terminals represents the rate of heat flow through this area (40 × 40 cm). Such layers cover the entire inner surface of the calorimeter. From the two terminals of the entire chain a potential is obtained which represents the total radiated and conducted-convected heat loss.

in 1958, with the Gradient Layer Calorimeter of the U. S. Navy at Bethesda ([8]) (fig. 7).

With this instrument our search began for reproducible relations between the responses—losses or gains of heat—and the stimuli of thermoregulation—temperatures at the surface or in the interior of the body. First it was found impossible in these attempts to discover meaningful and reproducible relations between the response of sweating and temperature as a stimulus. Neither with skin temperature nor with rectal temperature was the response of sweating found to be related in a reproducible manner (fig. 8 and 10, A).
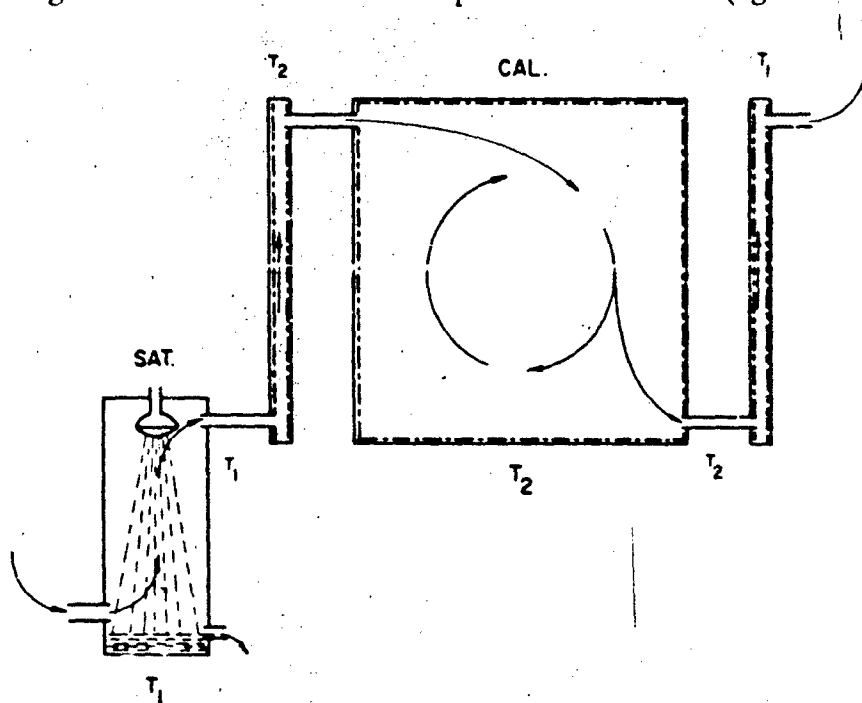

FIG. 5. — *A ventilatory circuit permits gradient layer calorimetry of circulating air.* The air passes through a saturator *(SAT)*. It enters and leaves the measuring system 100 % moist, at low temperature T_1. Added enthalpy from the subject in an environment of higher temperature, T_2, in the calorimeter, is measured as a difference in potentials from the gradient layers (broken lines) in the two plate-calorimeters. The excess moisture is condensed in the second plate, where the enthalpy change is recorded.

This experience changed with the introduction of another new method. With cranial (tympanic) thermometry ([9, 10]) (fig. 9), definite relations were observed ([9]) as shown in figure 10, B.

Comparison between tympanic and rectal temperature recordings (fig. 11, A-D) explains why rectal measurements had failed to provide the physiologist with meaningful information on internal temperature. In the rectum, where no thermoregulatory centers and no thermoreceptive structures of significance have been postulated of observed, temperature deviates widely from temperatures in the cranium (where structures of prime importance for thermoregulation are known to be located). On the other hand the patterns of cranial temperature variations are alike, regardless of where inside the
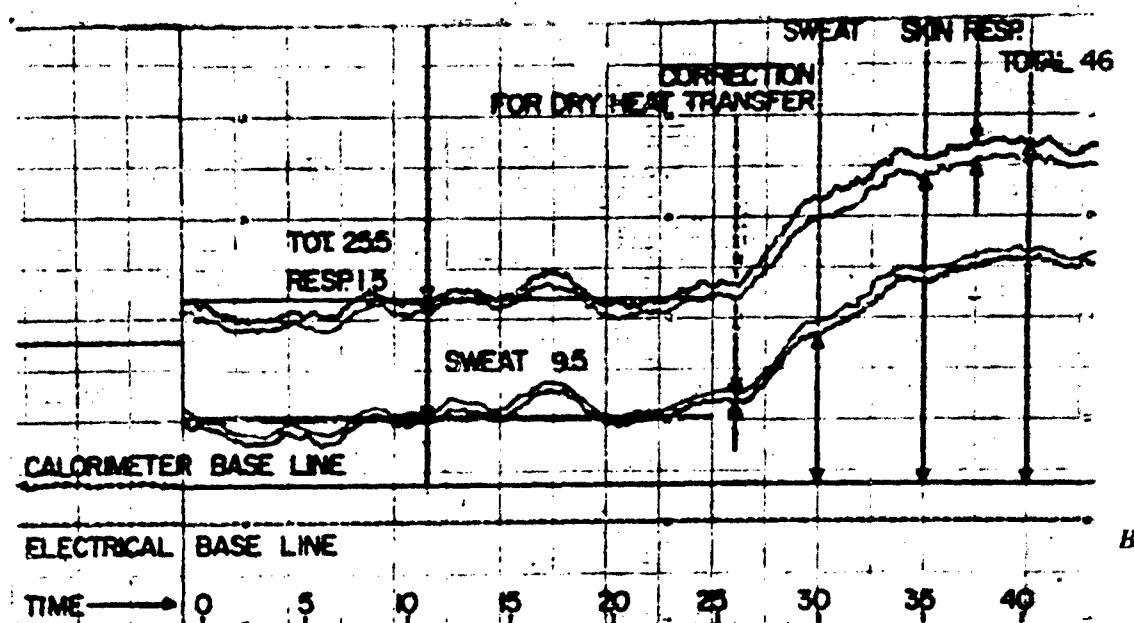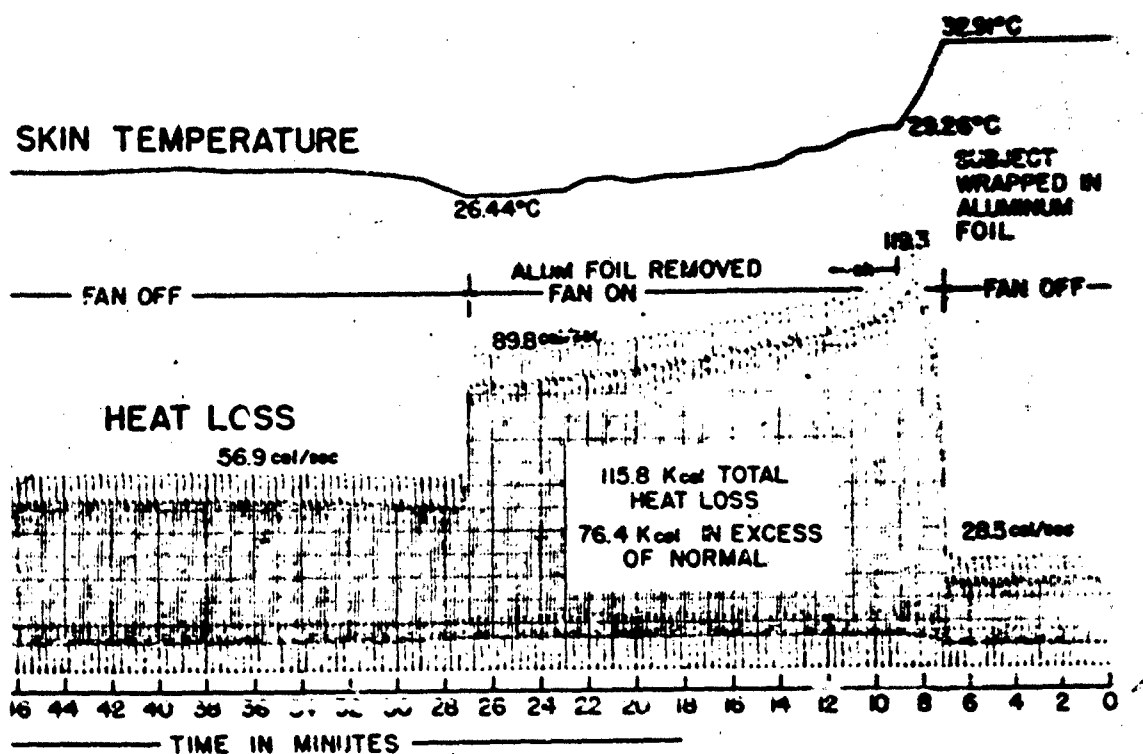
FIG. 6. — *Continuous recordings of human heat loss in the gradient layer calorimeter are shown.*

The upper recording *(A)* (reading from right to left) shows steadiness and uniformity of human heat loss in a cool environment (+10° C). The nude subject was first wrapped in aluminum foil. Removing the foil and introducing a forced convection raised the heat loss rate instantaneously from 28.5 to 119 cal/sec. Note the speed of response of the instrument to instantaneous changes, when heat loss is increased or lowered by introduction or elimination of forced convection or radiation.

Lower figure *(B)*, reading from left to right, shows heat loss in a warm environment (+30° C). The upper, narrow band is respiratory heat loss, moderately increased during exercise. The middle band is heat lost by radiation and conduction-convection, practically unchanged between rest and exercise. The lower band is evaporative, (sweating) heat loss. Evaporation increases during exercise from 9.5 to 30 cal/sec, raising the total heat loss from 25.5° C to 46 cal/sec. The irregularities in heat loss rate are caused by bursts of sweating.

FIG. 7. — *Interior view of the gradient layer calorimeter at Bethesda.* Subject is lying on metal screens in light frame, suspended on nylon strings. Gradient layers are covered with anodized aluminum foil of shining appearance, practically black for infrared radiation. Black-body geometry prevents loss of small reflected fraction.
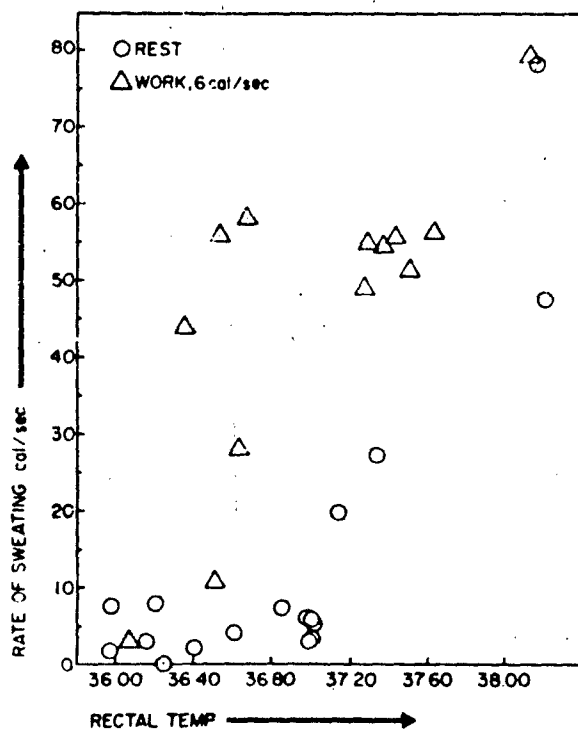

FIG. 8.

Relations of rectal temperature with sweating rates are erratic. Observations during exercise (triangles) are displaced to the left from resting observations (circles) because rectal temperature is lagging far behind cranial temperature when heat production rises.

cranium the measurements are taken (fig. 12). Sites as distant from each other as the suborbital region and the retropharyngeal recess of Rosenmueller (fig. 13) permit readings that differ only by a few hundredths of one degree C, in spite of rapid transients (fig. 13). At the tympanic membrane, the only « dry » site of measurement (fig. 9), temperatures are found somewhat higher than at the mucous wet surfaces of the other measuring locations. Nevertheless, aside from a slower response, there was no difference in the
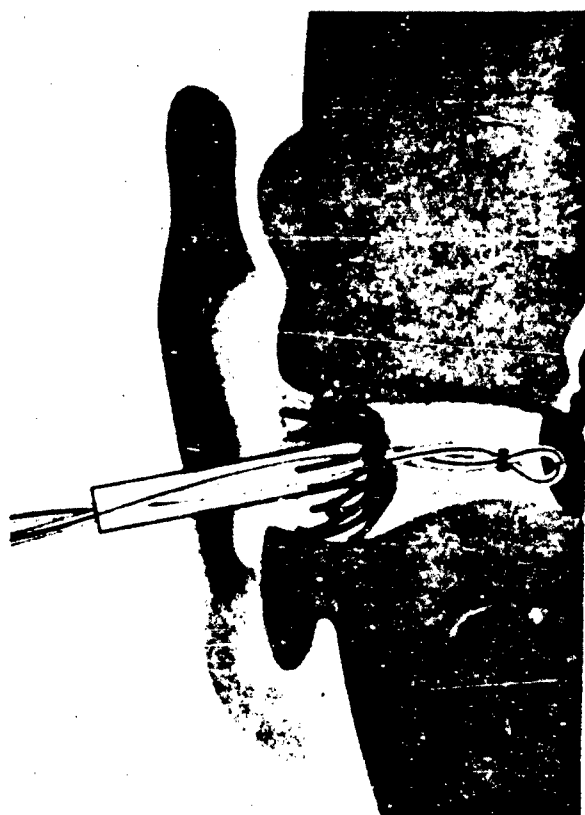
FIG. 9. — *Tympanic thermometer consists of disposable thermocouple in a loop of constantan and copper wires.* Bristles retain the soft probe in position for direct touch and gentle pressure.

patterns; and tympanic measurements were adopted as the method of our choice.

Throughout our study of human thermoregulation, cranial measurements of temperature have served as a guide in unknown areas not otherwise accessible on man; as the procedures of experimental surgery cannot be applied. With cranial instead of rectal measurements the advantages of gradient layer calorimetry can be realized. The two methods have comparable time-characteristics; the tympanic thermometer in measuring variations of internal cranial temperatures (potential stimuli), and the calorimeter in measuring sudden changes of heat loss rates (responses).
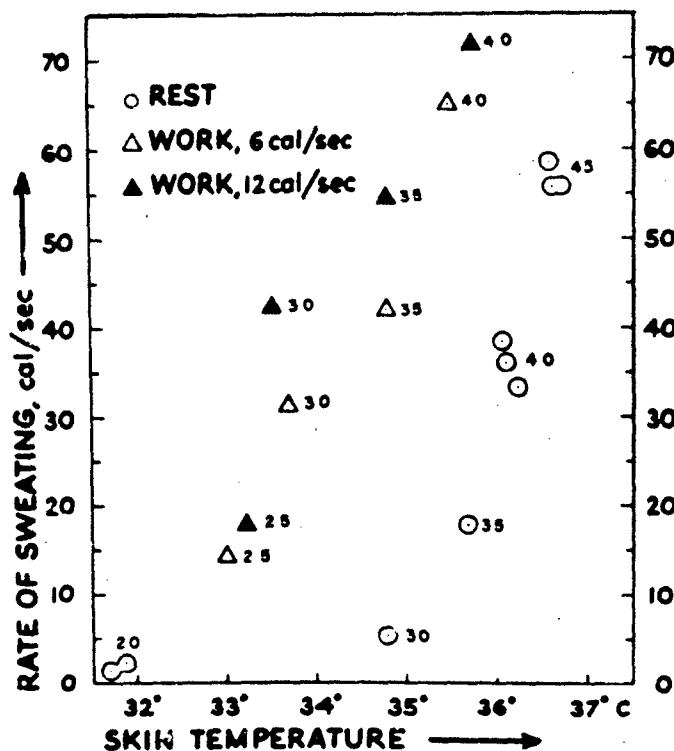
Fig. 10 A.

Steady rates of sweating obser- ved during exercice (trian- gles) or rest (circles) at widely varied levels of environmental temperature (figures at symbols) are not reproducibly related to skin temperature as a possible sti- mulus. The left-and upward shift of working observations is caused by the relative ele- vation of cranial internal temperatures during exercise.

Fig. 10 B.

Steady rates of sweating obser- ved during exercise (trian- gles) or rest (circles) are reproducibly related to cra- nial internal temperature (ordinate) inspite of large differences in skin tempera- ture (figures at symbols). The measurements are the same in figures 10 A and B. The figures at symbols (environmental and skin temperatures) apply to both illustrations and can be iden- tified from positions on the ordinate, for reproduction in other laboratories.
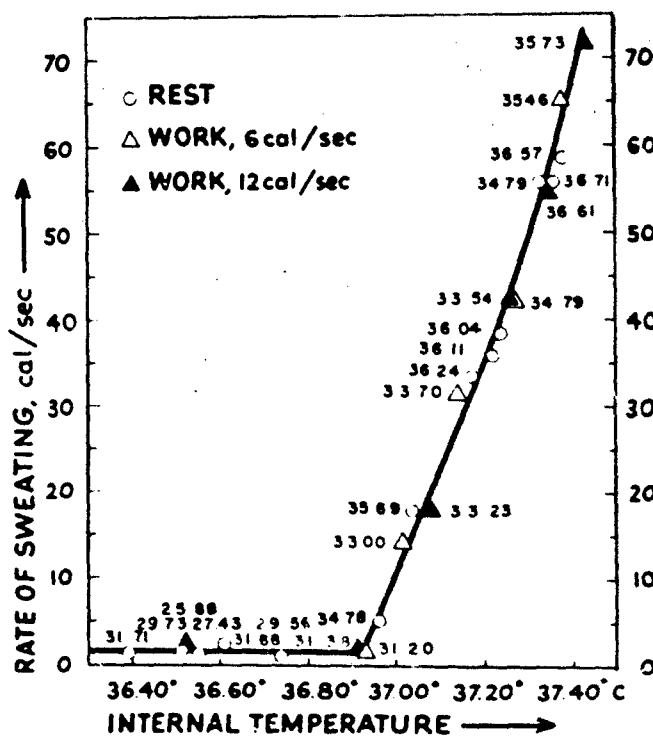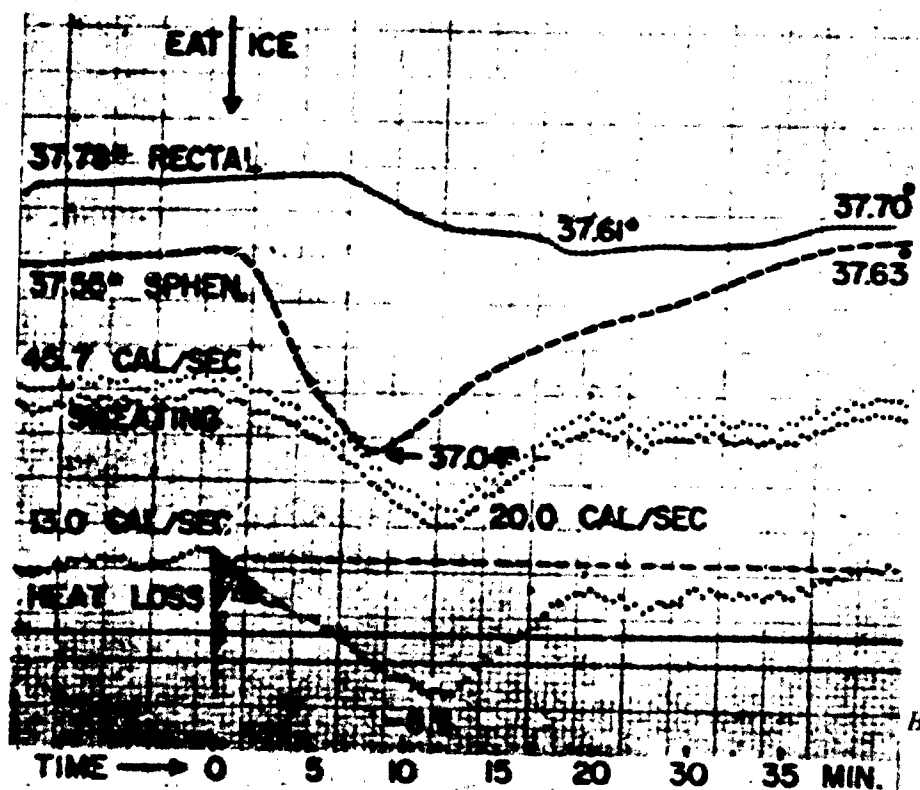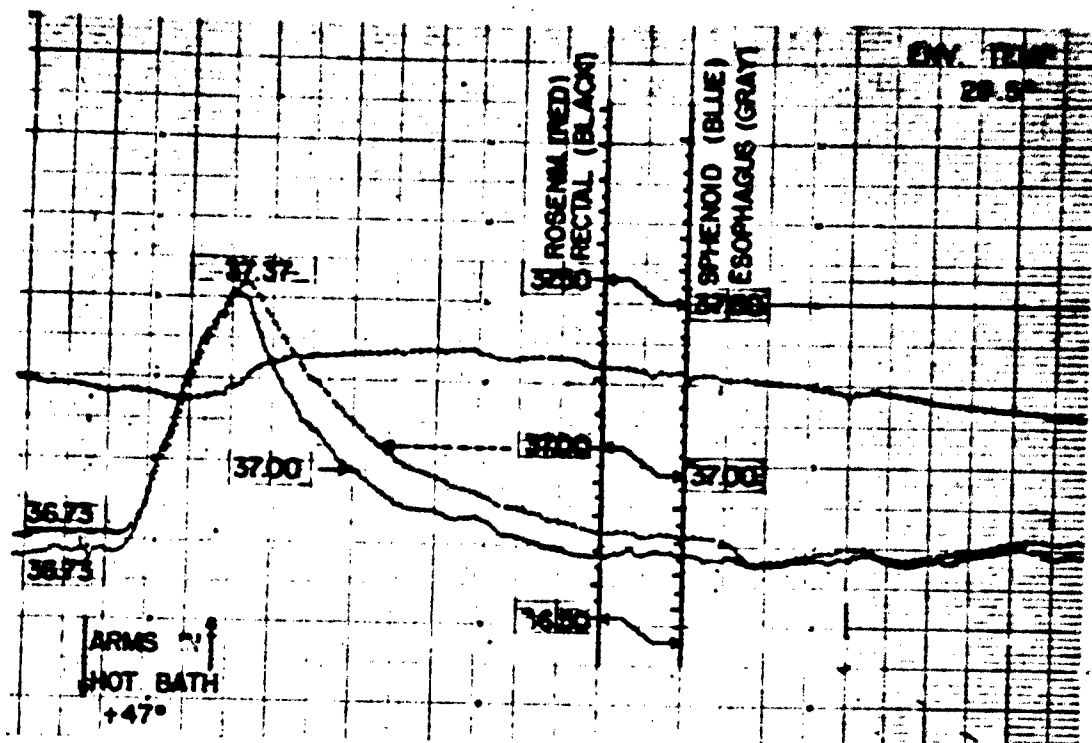
Fig. 11. — *Deviations of rectal temperature
from cranial internal temperatures observed.*

(A) When both arms of subject were immersed in 45° C water.

(B) When 250 g of sherbet ice were orally ingested.
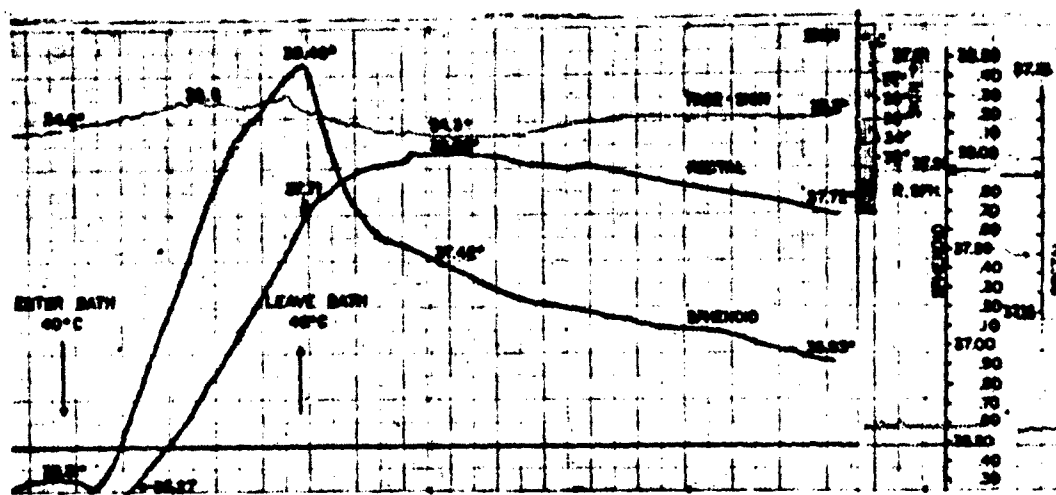
C
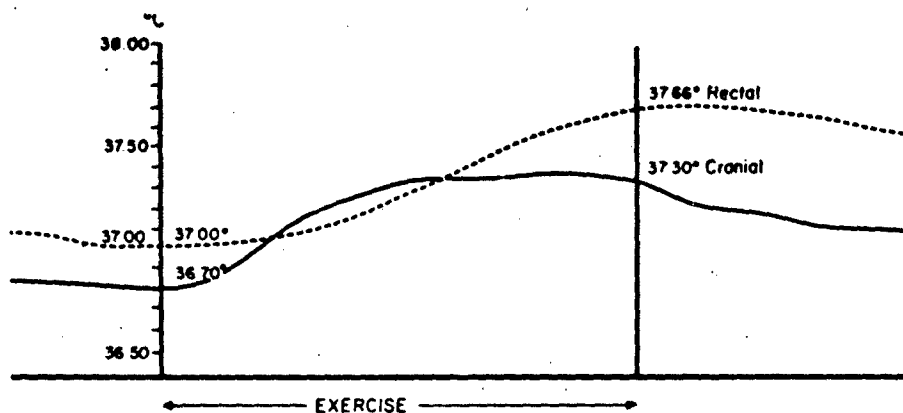
D

Fig. 11 — *Deviations of rectal temperature
from cranial internal temperature observed* (suite).

(C) When the subject entered and left a 40° C bath.

(D) During 45 minutes of exercise with a metabolic rate of 55 cal/sec
(20 cal/sec at rest).

PHYSICAL THERMOREGULATION

With rapidly recording calorimetry we found that the relations between cranial internal temperature and evaporative heat loss are concordant (fig. 14, *A, B, D*), and indicative of a true stimulus response-relationship, regardless of the external or internal application of thermal stress ([9, 11]). We found, conversely, that the relations between skin temperature and sweating are disconcordant (fig. 14, *C* and *E*) paradoxal and antihomeostatic, whenever the natural, coincidental connection between common trends of skin temperature and internal temperature is broken. In figure 14 *A* the rate of sweating parallels, not the suddenly changing environmental temperature (after
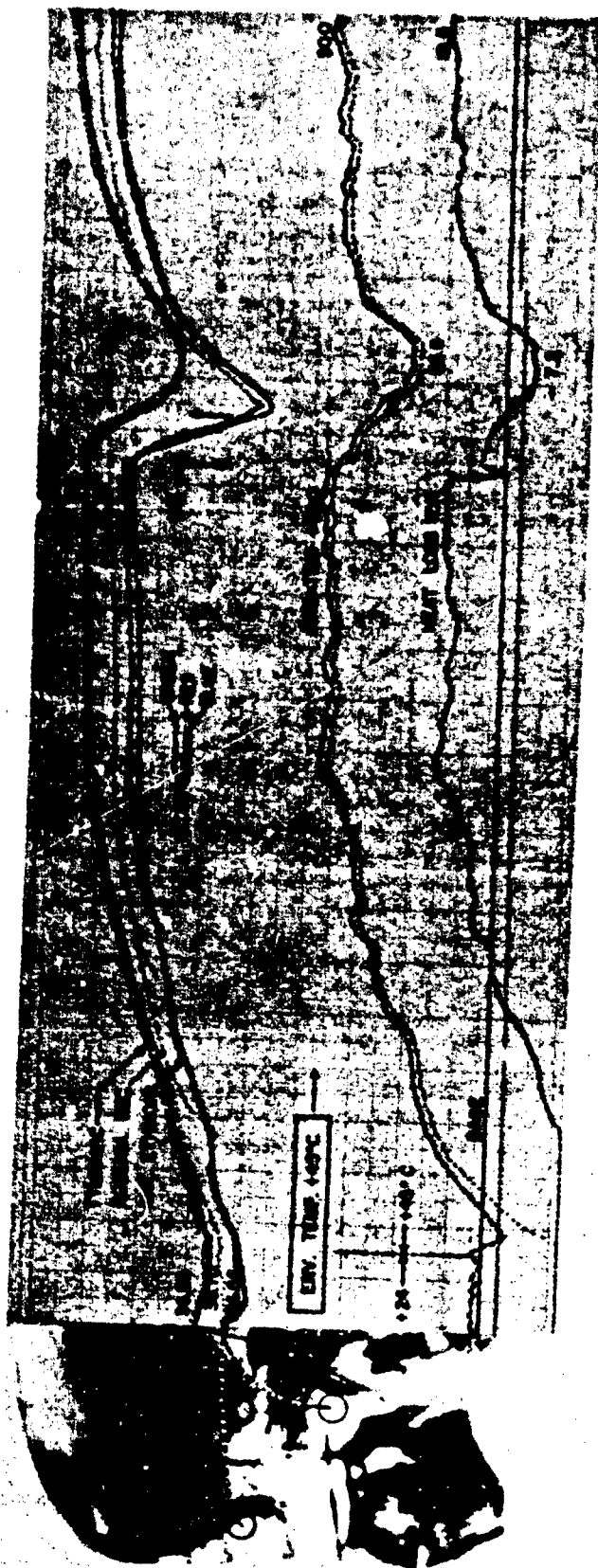
FIG. 12. — *Cranial temperatures were recorded from various cranial locations after transition from 24° C to 45° C environment, and after eating 250 grams of ice. The patterns are alike, regardless of where in the cranium the probe was located (compare figure 13). Rates of sweating-heat loss and cranial internal temperatures show concordant patterns. The tympanic reading is slightly higher and more inert than sinus readings.*

instantaneous transfer from 25 to 45° C), but the gradual increase of cranial internal temperature. The same parallelism, is observed after internal stimulation, in the second part of the experiment, where cooling of the stomach by ingestion of ice led to a sharp reduction of both, cranial temperature and the rate of sweating. During such an event skin temperature paradoxically, does not fall. It rises sharply, as demonstrated repeatedly in figure 14, *E*, whereas cranial internal temperature and sweating show again concordant changes (fig. 14, *D*). A similar relationship is observed after the onset of

Fig. 13. — *X-ray of thermocouples in various locations* (Subject T. H. B.).

exercise, with sharply discordant courses of skin temperature and sweating in figure 14, *C*, and a concordant course of cranial temperature and sweating in figure 14, *B* (the latter relation is less perfect than the others; possibly due to peculiar « non-thermal » effects during exercise, observed recently by Van Beaumont ([12]) and to certain characteristics of central warm-sensitive neurons on which Nakayama et al. ([13]) observed an « abrupt decrease in firing-rate with cessation of heating »).

From the discordant and paradoxical characteristics in figures 14, *C* and *E*,

Fig. 14. — *Concordant patterns of sweating rate and cranial internal temperatures and discordant patterns of sweating and skin temperatures are observed.* (*A*) after change from 24 to 45° C environment and eating ice, (*B* and *C*) during exercise.
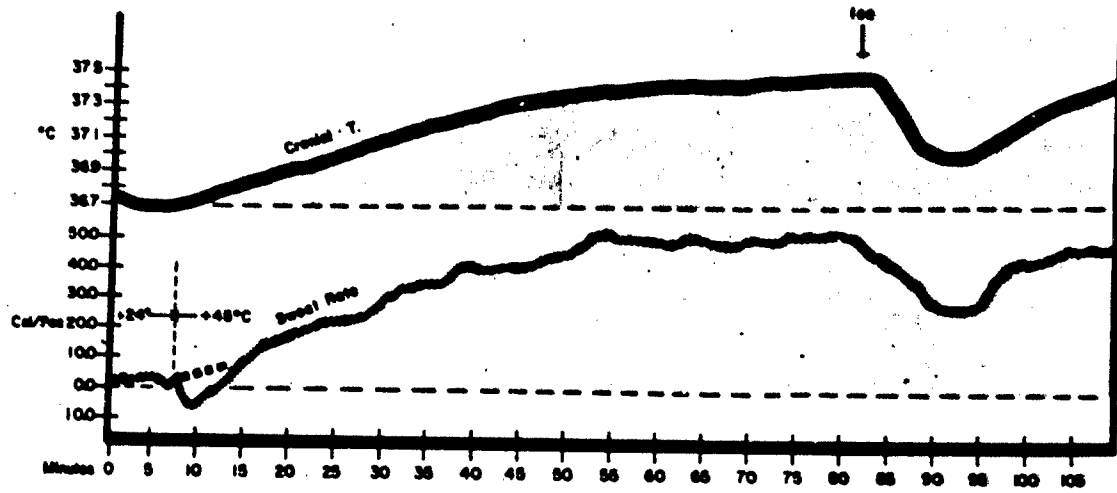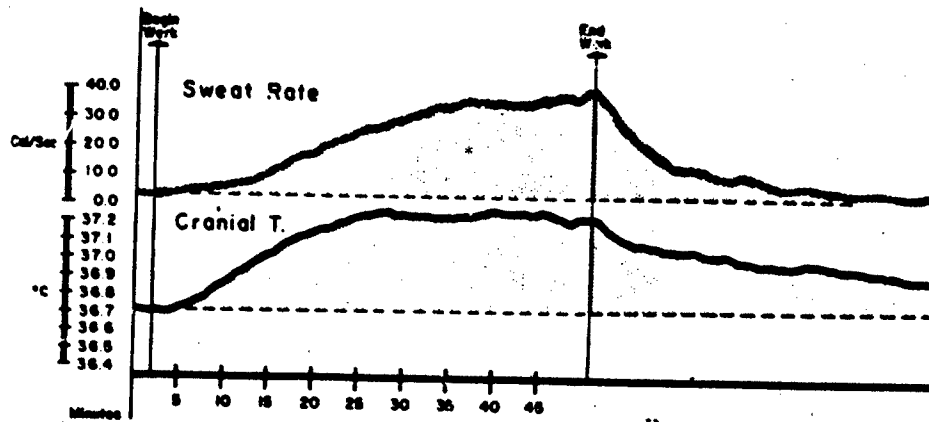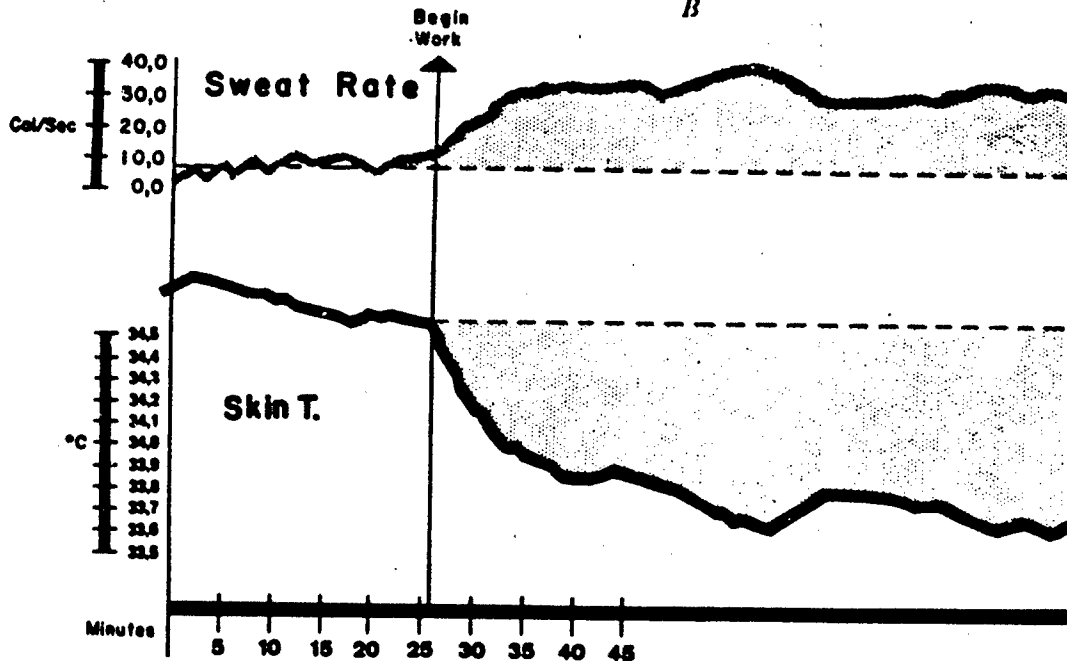
FIG. 14, *A, B, C.*
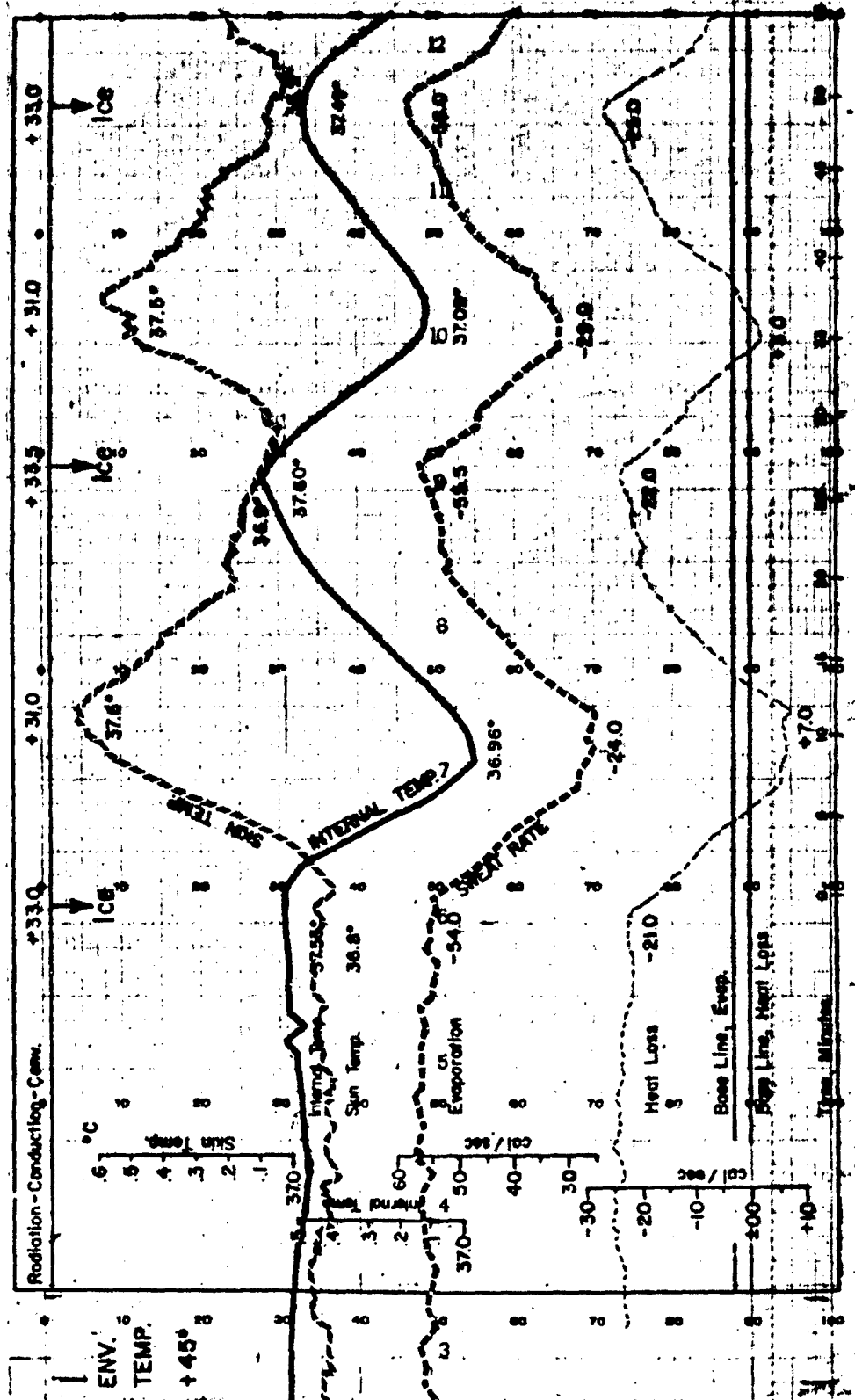
Fig. 14 (suite). — Concordant patterns of sweating rate of cranial internal temperatures and discordants patterns of sweating and skin temperatures are observed. (D) During repeated oral ingestion of ice.

it appears that the relation between skin temperature and sweating cannot possibly be a physiological relationship of stimulus and response. The relation is caused physically. When the centers are cooled by eating ice, the skin, paradoxically, is warmed as a consequence of the sharp reduction

of sweating in a warm environment. When the centers are warmed by exercise, the skin becomes cool as a result of the increase in sweating. On the other hand, the relations which we found between internal cranial temperature and sweating in figures 14, *A, B* and *D*, were those that are to be expected, when sweating is a response to warm-stimulation of a sensor in central position.

The classical theory, that sweating was elicited by warm-reception at the skin (and modified by a temperature dependent readiness of the centers for synaptic transmission), has not been borne out by these experiments. If
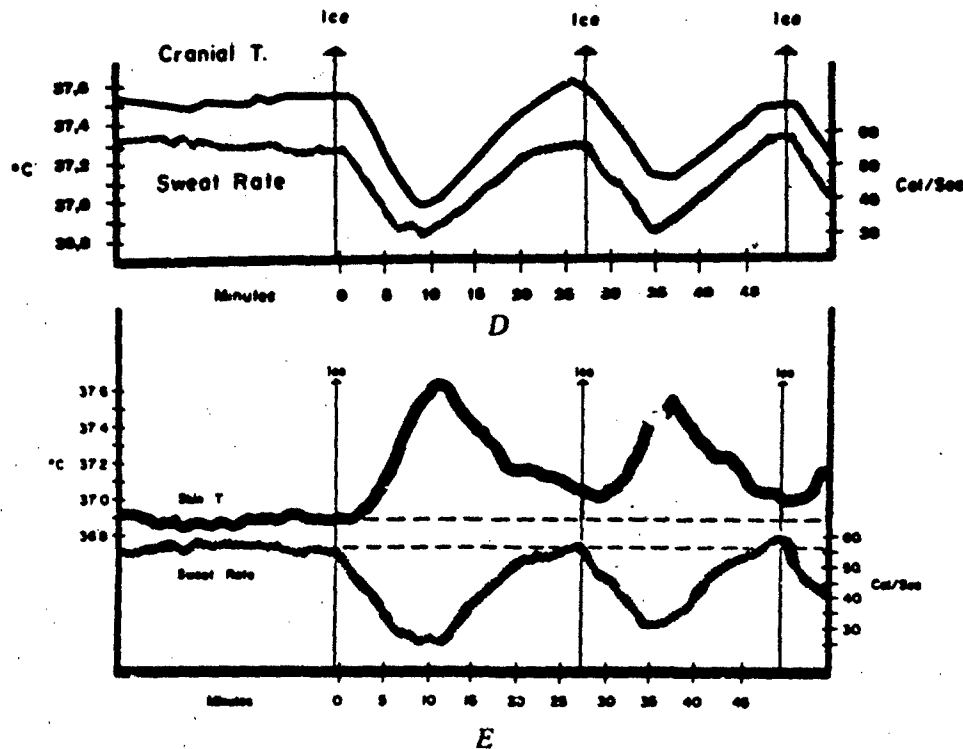
Fig. 14 *(suite)*. — *Concordant patterns of sweating rate and cranial internal temperatures, (D), and discordant patterns of sweating and skin temperatures, (E), are observed during repeated oral ingestion of ice.*

indeed the response of sweating depended on skin warm-reception, the outpouring of sweat upon the very site of temperature-reception would frustrate the principal servo-mechanism of physical temperature regulation by « positive feedback. » The stimulus at the skin would be quenched, before the cooling-effect could be « fed-back » to the centers, when it is most urgently needed, at high internal temperature during work in hot environments. We shall see later, that in chemical as well as in physical heat regulation the effector sites of corrective action are spatially removed as they should be, from the sites of temperature-reception proper.

While transient changes (fig. 14) demonstrate more directly the concordant or discordant relations between various stimuli of temperature and sweating of man, it is important to demonstrate these relations also in steady states, during sustained external or internal thermal stresses and over a wide range of

different environments in which physical thermoregulation may be active. In figure 10, *A* and *B*, steady state sweating rates are shown as measured on eight different days with one lean subject at rest or during exercise in environments ranging from +20 to +45° C (Further measurements were made at +10° C with no sweating observed) in the gradient calorimeter. The data were first plotted against skin temperatures in figure 10, *A*. A disrupted relationship appears. There is a pronounced left—and upward shift of observations made during exercise, as compared with sweating rates observed at rest. At any given temperature of the *skin* the *internal* temperature of the man at work is higher than the internal temperature of the man at rest. This causes the left—or upward—shift of sweat rates during exercise in figure 10, *A*, and demonstrates again the dependency of sweating on central temperature.

This relation appears more clearly when the same measurements of sweating are plotted against cranial internal temperature (fig. 10, *B*). Although at any given cranial internal temperature the skin temperature of the man is lower when he works, no right—or downward—shift of sweating rates is observed during exercise. Under the physiological conditions of these experiments (a lean subject, environments between 10 and 45° C, and work loads up to 2.5 BMR), no influence of skin temperature on sweating is visible although skin temperatures differed by 1.5° C to 2° C during work, compared with the skin temperatures at rest.

Under similar conditions, Belding ([14]) made essentially the same observations, though with more scattering, in an open warm room. Minard ([15]) found higher sweating rates on the working man who has a cooler skin. Attempts to prove a driving influence of skin temperature on sweating in the warm-range have thus been unsuccessful in this and other laboratories under physiological conditions of external or internal stress in the warm-range. This did however, not discourage continued efforts aimed at disproving our results of figure 10, *B*. Eventually, Bullard ([16]) succeeded in demonstrating an influence of local, not general skin temperature on local, not general sweating. He separated skin temperature from its physiological relations with internal temperature by as much as 6° C (whereas in our experiments skin temperature-differences between rest and exercise had been 1.5 to 2° C). Bullard demonstrated, that when relations are artificially separated beyond physiological conditions, the activity of sweat glands is not indifferent to their own temperature. This is not unexpected, when circulatory effects, metabolic requirements and possibly other factors of sweat gland activity are duly considered. Whatever these influences of skin temperature upon sweating may be, they have not obscured the basic stimulus response-relation between internal cranial temperature and sweating as demonstrated in figures 10, *B*, 15, *B* and 24.

Another influence of skin temperature on sweating was found in this laboratory earlier ([17]). When a rather obese subject is internally warmed by strenuous exercise in a relatively cold environment, he may become internally overheated, with a cold skin. His thermoregulation receives conflicting messages on temperature from central and peripheral sensors. Under

this condition, in the skin temperature-range below 33° C, where cold-receptors of the skin exhibit elevated firing rates and where they elicit chemical thermoregulation, a dramatic inhibition of sweating is observed (fig. 15). Thereby, a simultaneous and antagonistic excitation of sweating and shivering is prevented, when paradoxically, man is centially overheated
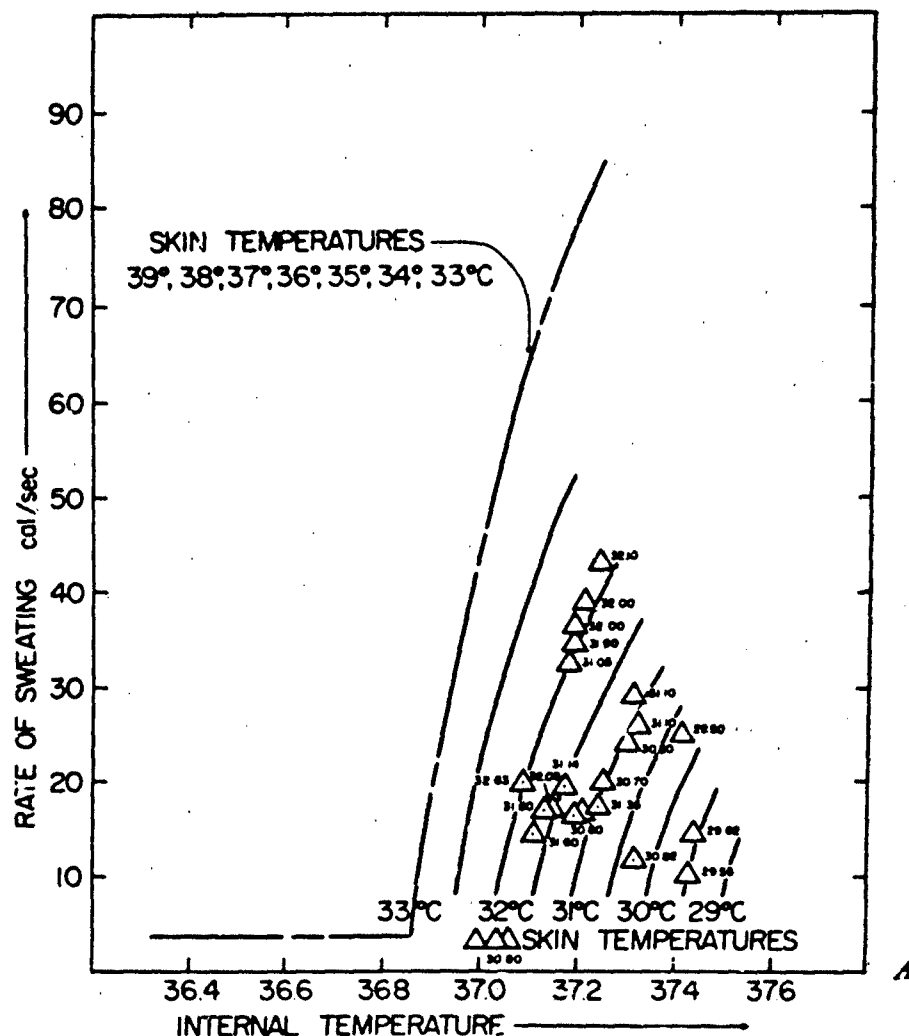
Fig. 15. — *The inhibition of sweating during cold-reception at the skin is demonstrated with steady state sweating rates plotted in* (A) *and* (B) *against tympanic tempe . ture, and in* (C) *against skin temperature.* Below the threshold of skin cold receptors *(A)* sweating is partly or wholly inhibited. Above the cold receptor threshold *(B)* sweating follows tympanic temperature. The skin-plot *(C)* shows independence of sweating from skin temperature in the warm-range (tympanic isotherms are parallels to abscissae) and inhibition of sweating at low skin temperature (slanting tympanic isotherms at left).

and externally cooled. This mechanism is « anti-homeostatic. » It prevents at least temporarily the return of an aberrant central temperature to the norm. Nervous pathways of this inhibition are as yet unknown. A possible explanation as a direct effect of temperature on sweat glands has not yet

been ruled out, although the strength of the effect and its beginning at the threshold of cold-receptors make such an alternative explanation improbable.

In the v ..rm-range, where the cold-receptors are inactive, the faithful relation between sweating and cranial internal temperature of man is again observed
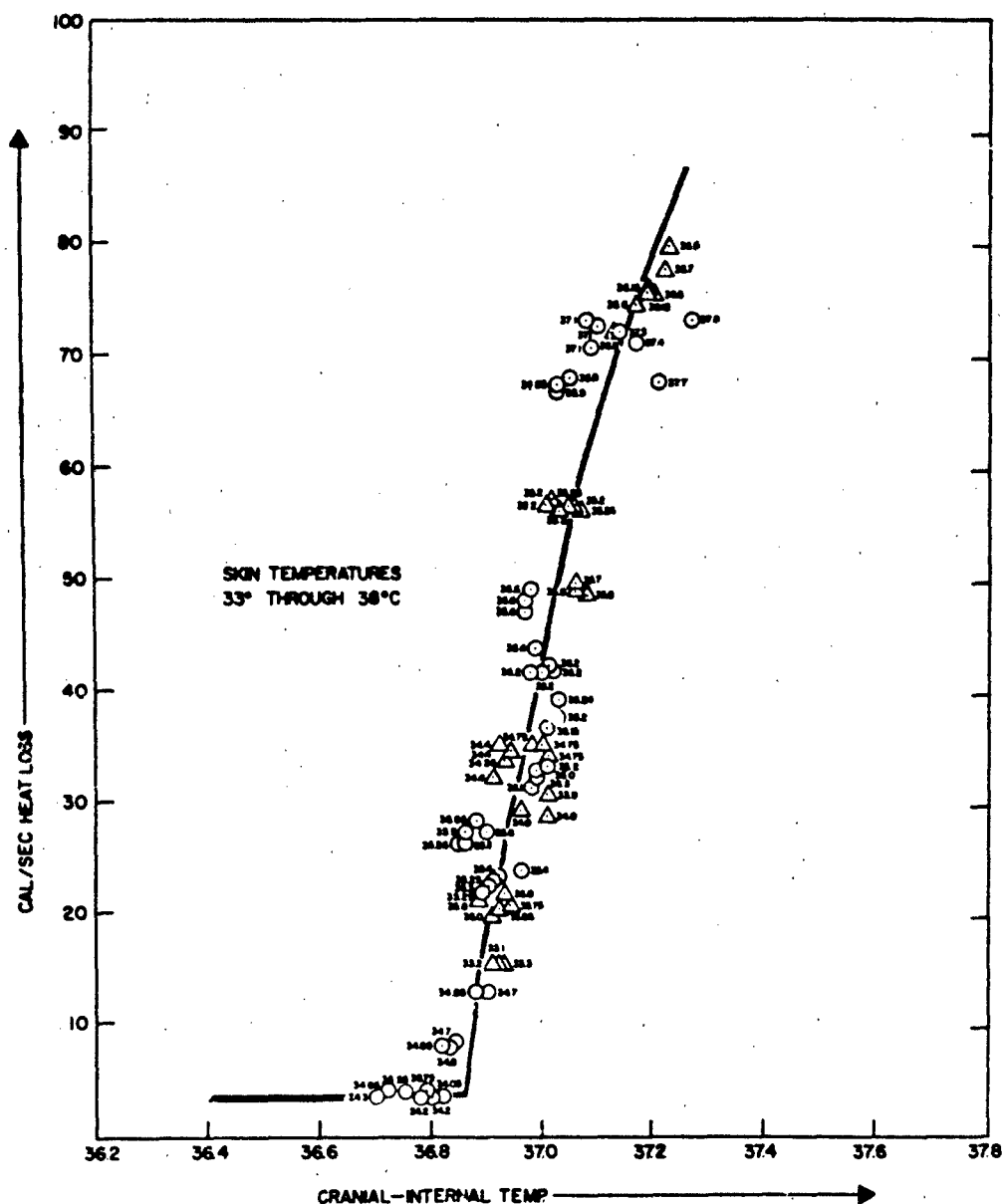
FIG. 15 *(suite)*. — *(B)* Voir légende page 343.

(fig. 15, B). In figures 10, B, 15, B, and 24 the central origin of sweating is demonstrated with three different individuals, and more fully documented than in earlier publications, to facilitate repetition of these calorimetric measurements in other laboratories. Our conclusion was since 1959, and remains after thorough discussion, that sweating is centrally, not peripherally elicited and that it is independent of driving warm-impulses from the skin. Therefore,

the seat of central elicitation of sweating, being independent of a synaptic transmission of peripheral impulses, must be a terminal sensory organ for temperature-reception : a « *temperature-eye* », comparable in its function and efficiency to the anatomically related retina, our optical receptor. This temperature-eye performs as a « *human thermostat.* » It holds by way of heat-
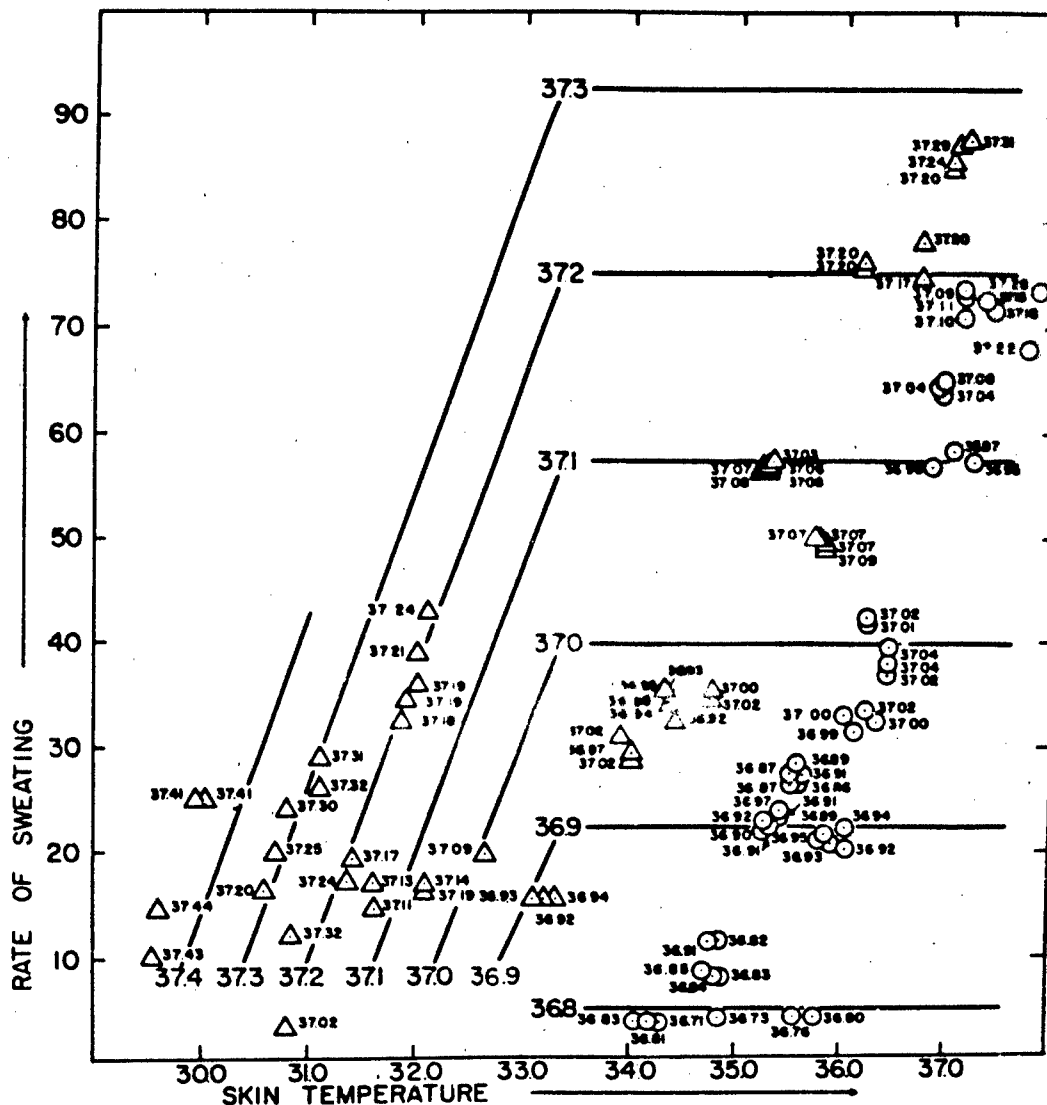
Fig. 15 *(suite)*. — *(C)* Voir légende page 343.

loss-responses the central temperature of man in warm environment close to a sharply determined setpoint. The setpoint is seen as reflecting temperature-characteristics of an unknown molecular component in the structure of the sensory neurons, which undergoes certain transitions when temperature rises above, or falls below the setpoint. The setpoint may be shifted through the effects of pyrogens ([1K]) or by other, more subtle chemical influences of various origins upon the temperature-dependent molecular system (comparable to freezing point-depression in physicochemical systems).

Immediately it was objected, that histological or other proof would be required to substantiate the view of a terminal sensory organ for temperature in the hypothalamus. Evidence of a non-histological nature came in rapid succession with two outstanding studies in 1962 and 1964 : First Nakayama et al. ([13]) and later Hardy et al. ([19]), have demonstrated spike-action potentials of temperature-dependent frequency from neurons in the preoptic region. Slow temperature-dependent potentials had been discovered even earlier by C. Von Euler ([20]), and the classical discovery of Barbour ([21]) that the anterior hypothalamus responds to thermal stimulation, is appropriately quoted at this point. Andersson ([22]) exerted artificial control over this system on goats with electrical stimulation by which he could depress the internal temperature of the animals to 29.5° C. He obtained a more succinct delineation of the area which had been outlined earlier in the classical work of Magoun et al. ([23]). To the findings of Nakayama and of Hardy more detailed reference will be made later.

For mutual understanding between the thermophysiologists working with animals or man, it seems important to recall that the thermal homeostasis of man differs basically from that of other species. Certain means of temperature control are highly developed in man, while other mechanisms, important to animals, play only minor rôles, or have been abandoned. From multiple available choices an efficient system appears to have evolv I by selection. The following differences are important to observe : Unlike birds and mammals, man does not physically thermoregulate by increased pulmonary ventilation. Both, Richet's *polypnée centrale* and Richet's *polypnée réflexe* including its behavioral aspect are practically absent. The function of these mechanisms is replaced by sweating of the fur-less human skin. The sweating of man may be described as a parallel to *polypnée centrale*. The existence of reflex sweating, a parallel to *polypnée réflexe*, is unclarified and makes at best a limited contribution.

Vasodilatation. — With simultaneous measurements of skin temperature and internal temperature the gradient layer calorimeter permits the measurement of thermal conductance

$$C = \frac{Q}{T_i - T_s} \quad [\text{cal sec}^{-1} \text{ deg}^{-1}]$$

where Q [cal/sec] is the heat loss from the skin, and T_i and T_s are internal and skin temperature [°C]. Conductance C is used as an index of the exchange of blood between the core of the body and the skin. Together with the rates of sweating from figure 10, B, the conductances measured in the same experiments are plotted in figure 16, A. It appears that the response of sweating is supported by a strong increase of peripheral circulation. Vasodilatation begins at the setpoint. It rises steeply with internal cranial temperature. Thus, it reveals a decisive central component of its origin. However, a considerable influence of skin temperature appears in figure 16, B, as a right—and downward shift of conductance measured during exercise. The

FIG. 16 *A*.

Vasodilatation in response to cranial internal warm-stimulation is demonstrated with plot of conductance against tympanic temperature. Vasodilatation and sweating appear co-ordinated. Setpoint=36.9° C. All observations of conductance were made at rest for this graph.
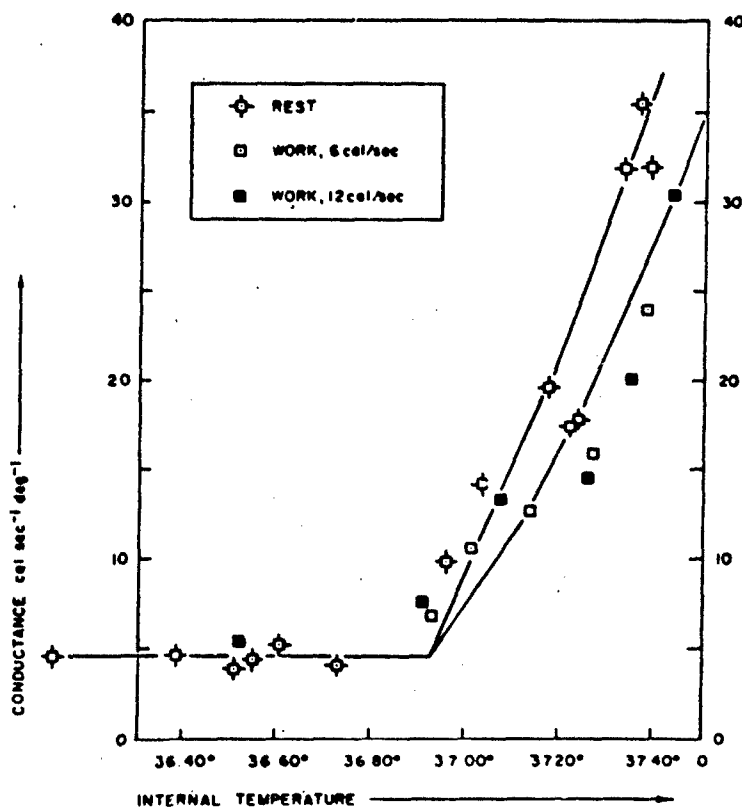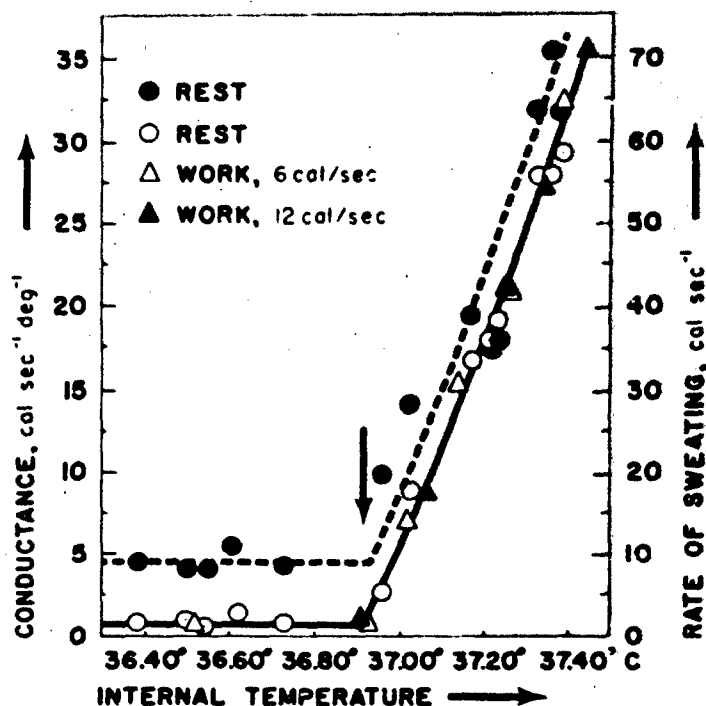

FIG. 16 *B.*

Rest-and exercise observations of conductance demonstrate a major influence of skin temperature (right-and downward shift of observations during exercise, where skin temperatures are relatively low).

latter observation is consistent with well known direct influences of temperature on peripheral vessels.

The vasodilatation observed, with sevenfold increase of peripheral bloodflow over basal rates, does not result in substantial losses of heat by radiation and conduction-convection. In warm environment these heat exchanges are usually gains, not losses. Vasodilatation, nevertheless, prevents that sweating cools the skin to a degree that would prevent evaporation of the sweat, and would lead to wasteful dripping. As a supporting mechanism of sweating, vasodilatation has first-rate significance.

While vasodilatation is based primarily on central warm-reception as a source of driving impulses, there is a strong peripheral component of multiple and not fully clarified origin. The importance of this peripheral component has been repeatedly and strongly emphasized in our work, begining with its first publication ([9]).

The peripheral component is clearly shown in figure 16, B. The central component appears to be closely correlated to the central elicitation of sweating, described above.

These findings illustrate in a quantitative manner, Claude Bernard's concepts of both the importance of vasomotor responses and the dominant control by the central nervous systems. With reference to the concept of a terminal sensory organ and human thermostat in the preoptic region, the investigative history of the anterior hypothalamic « heat loss center » should be recapitulated at this point. However, in references 9, 30, and 36, the prominent anatomical discoveries have been listed and discussed. The calorimetric observations described in this paper are consistent throughout with classical results of destruction, electrical stimulation and thermal stimulation of thermoregulatory centers and pathways and with the recorded temperature-dependent firing-rates of sensory neurons involved. These relations shall be discussed in more detail later.

CHEMICAL THERMOREGULATION

In chemical thermoregulation the effector mechanism of prime interest is shivering with metabolic production, not loss of heat. Here, direct calorimetry can be replaced by indirect calorimetry, with rapid and continuous measurements of oxygen consumption ([24, 25]). In this way, inertial delays introduced by the heat capacity of the body are avoided. Liberty is obtained to immerse subjects in stirred water baths of various temperatures, where the skin assumes practically the temperature of the water, and where not only skin temperatures but also internal temperatures can be manipulated at will, by pre-heating or cooling.

In the experiment of figure 17, the human subject was transferred from a bath of $37°$ C into another bath of $28°$ C, and then returned to a $36°$ C bath. As a result the oxygen consumption, index of the metabolic production of heat, rose suddenly from 290 to 850 milliliters per minute. In the indifferent

bath it returned swiftly to normal. No change of internal cranial temperature was observed during the short exposure. The effect upon metabolism must have been elicited from the skin, not from the centers.

In the experiment of figure 18, *A*. the experimental design was changed. The subject remained in cooler baths, during three consecutive transplace-
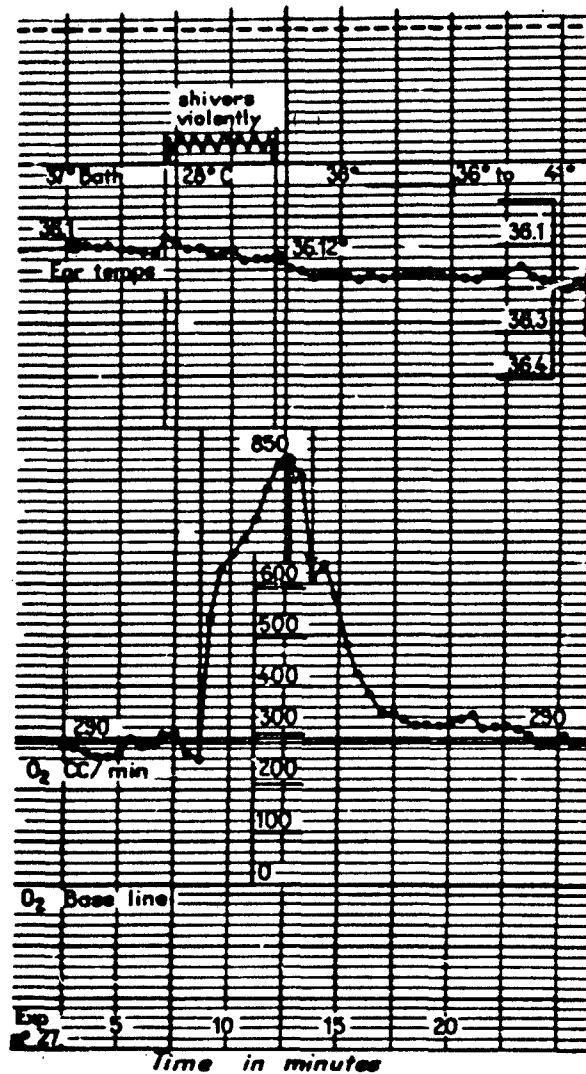
FIG. 17. — *Metabolic response to cold-stimulation of the skin was observed in temporary transfer from an indifferent* (36°C) *into a cool bath* (28°C) *in the absence of tympanic temperature changes.*

ments leading to lower skin temperatures in three steps (36 to 33; 35 to 32; 34 to 31° C). Each time the transition to a lower temperature was answered by a transient spike in oxygen-consumption. Such transient spikes are typical likewise of firing rates of cold-receptors in the tongue of the cat [Hensel and Zotterman [26]] and in the skin of man [Hensel and Boman [27]] in response to sudden cooling (fig. 18, *B*). Equally typical for both the firing-rates of
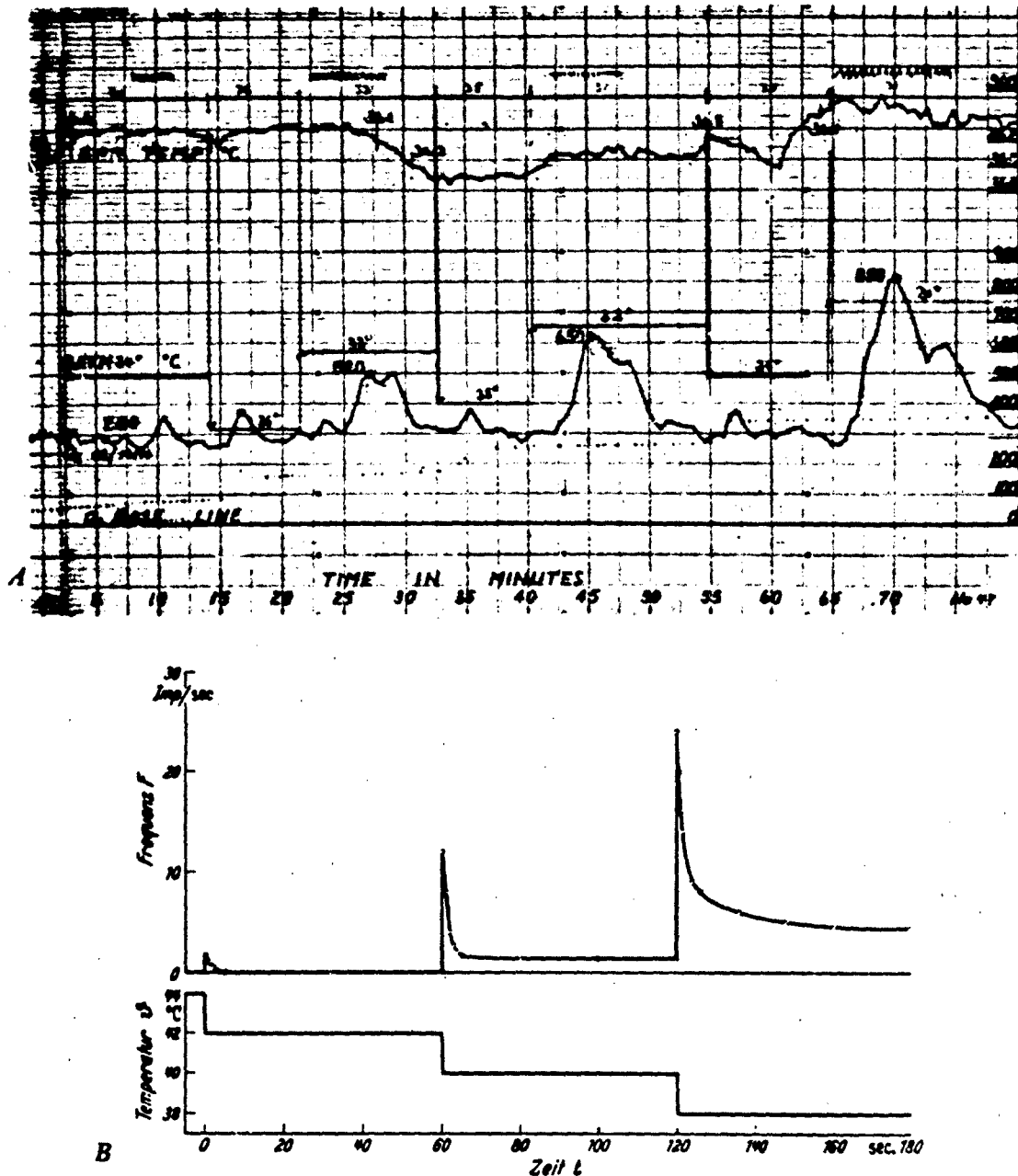
FIG. 18. — *Consistency of metabolic responses to cold in man* (A and C) *with temperature-dependent firing rates of cold-receptors* (B) *is demonstrated.* In *A*, at moderate cooling, metabolic responses are obtained only during transitions. In *C*, at lower levels of skin temperatures, metabolic rates in the steady state are also elevated. *B*, reproduced from Ref. 26, with permission of H. Hensel shows steady elevations of firing rates in response to elevated levels of receptor temperature and temporary elevations of firing rates during transitions.

cold-receptors of the skin and human oxygen consumption, is overshooting inhibition upon sudden warming (fig. 19, *A* and *B*). Analogies between electrophysiological and indirect calorimetric observations go further : In figure 18, *C*, with a lower range of temperature, the oxygen consumption rose not only in response to the *change*. It remained elevated in relation to the

lower *level* of skin temperature. The same phenomenon is observed with firing-rates of cold-receptors of the skin. They too respond to both, changes of temperature, and temperature as such (fig. 18, *B*).

Not only in transient responses to cooling and warming but likewise in steady responses to lowered levels of temperature, oxygen consumption of man and firing rates of cold receptors show analogy of their quantitative characteristics. Firing-rates of human receptors, observed by Hensel and Boman ([27]) are comparable in threshold and maximum of response, with the
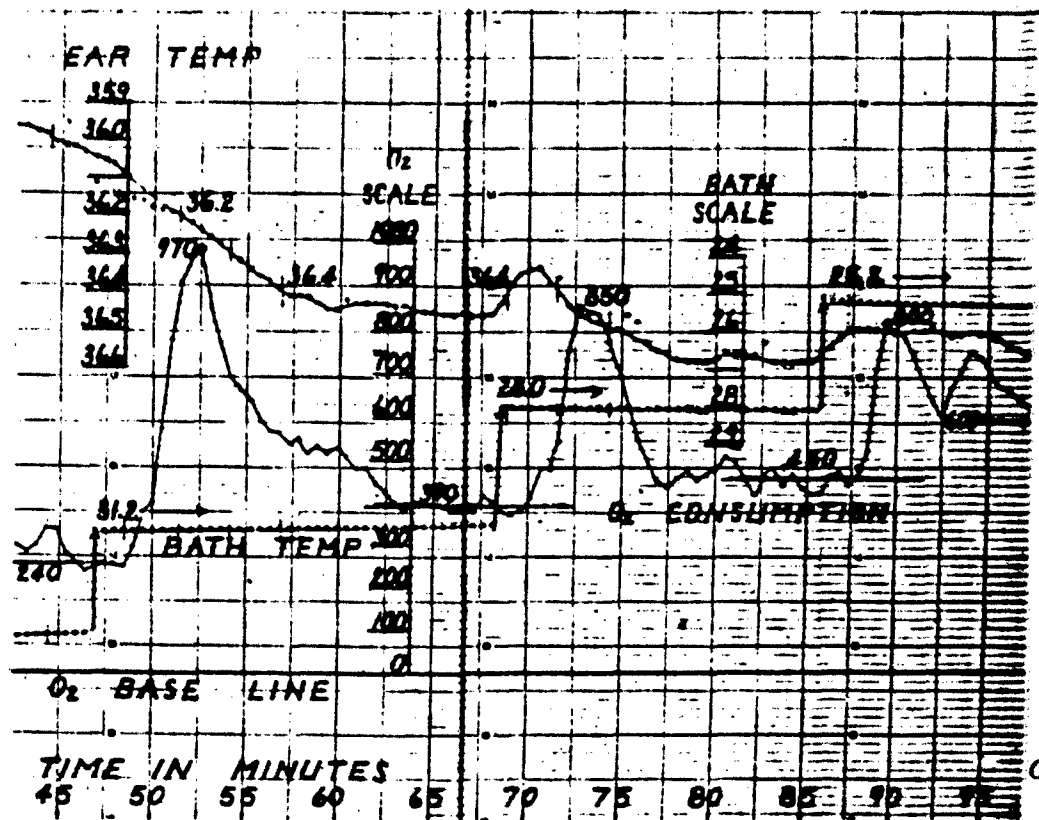
Fig. 18 *(suite)*. — *(C)* Voir légende page 350.

response by oxygen consumption to cold-stimulation of the entire skin of man (fig. 20, *A, B* and *C*).

Elevated levels of metabolism, responses to lowered steady levels of skin temperature, were investigated in a further series of experiments made on one man during a period of three months. Results are plotted in figures 21 and 22. Internal and cutaneous temperatures had been manipulated with the largest possible degree of independence. Skin temperatures were kept constant during measurements, and the initial transients after a transfer were disregarded in the plots. The purpose of the manipulation was to eliminate any coincidental relation between the temperatures of centers and periphery. Whatever meaningful relations might be found between oxygen consumption and either one of the two temperatures, skin or central, they could not be

A

Time (sec)
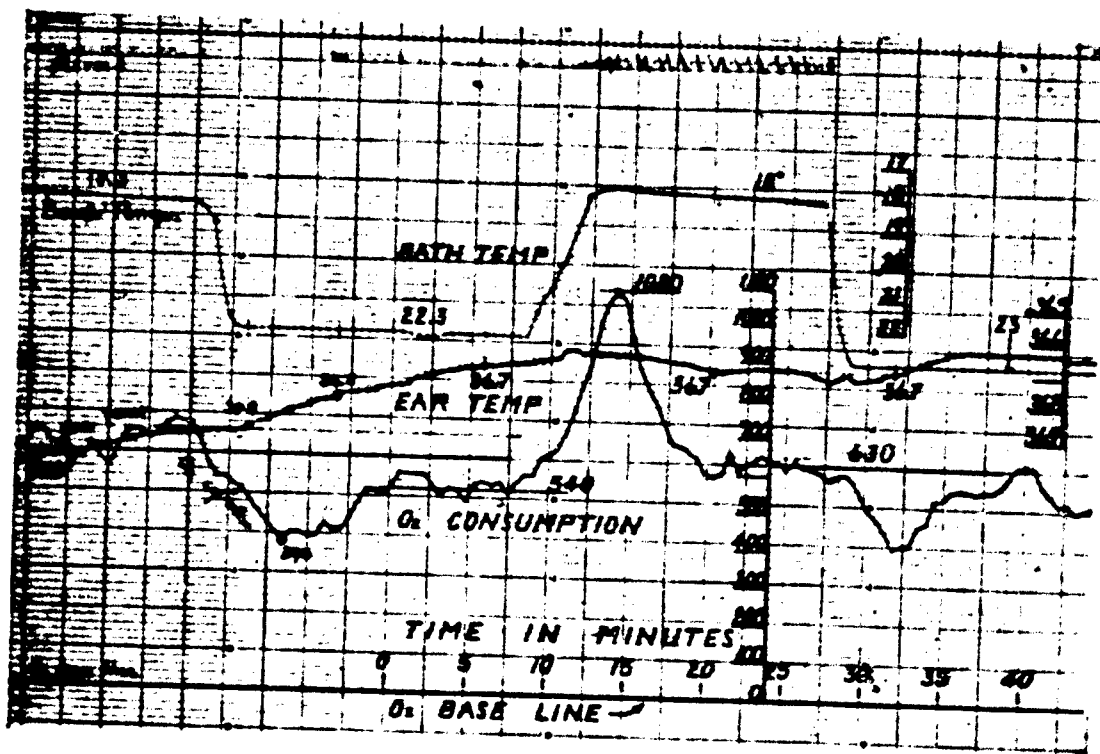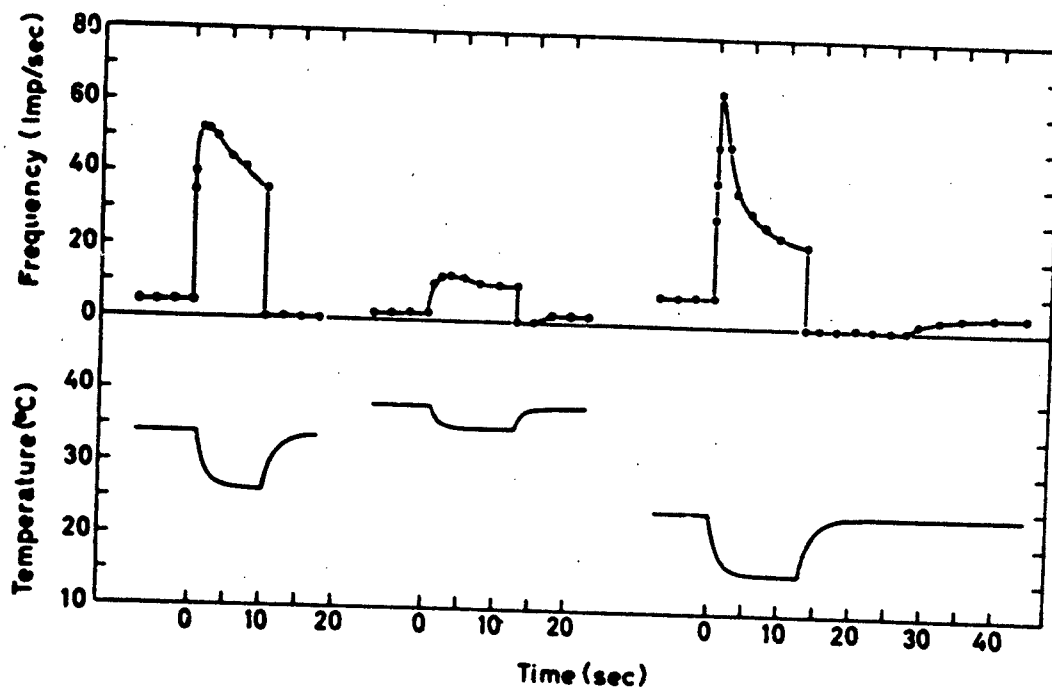
B

Fig. 19. — *A* and *B*. — *Rates of total human oxygen consumption and firing-rates of cold-receptors in the human skin both exhibit overshooting inhibition upon warming, and overshooting response upon cooling.* Firing rates *(B)* were observed by Hensel and Boman [27] and are reproduced by permission.
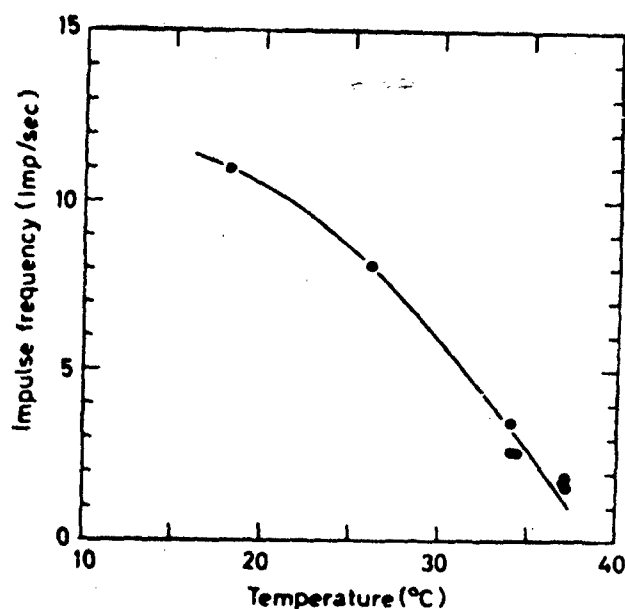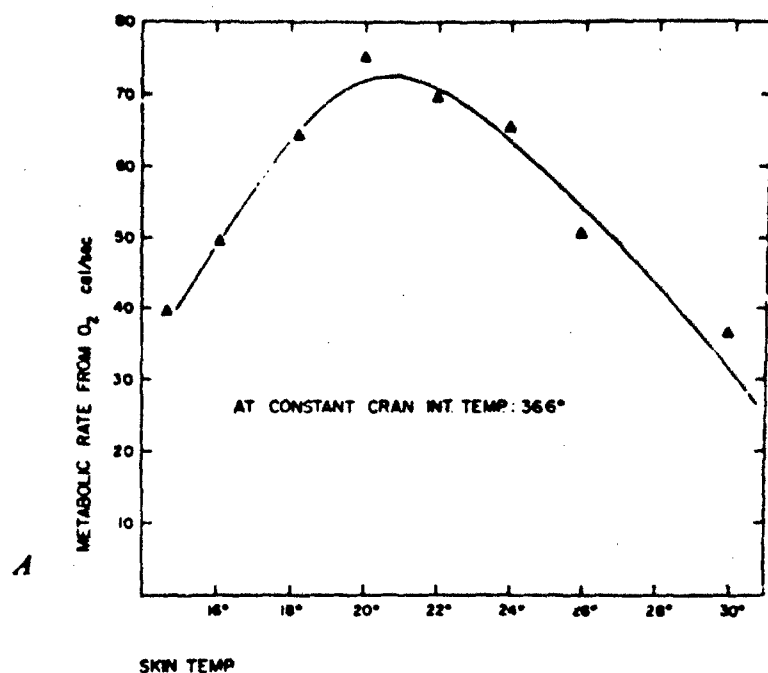
FIG. 20. — *Rates of human oxygen consumption* (A) *and firing-rates of human cold receptors* (B) *show consistent patterns, with maxima near 20°C.* In *(A)* the threshold is lowered from approx. 35°C to 32°C, by partial central inhibition (central temperature was 36.6°C for all plotted points). Similar patterns, with higher maxima, are shown in *(C)* with firing-rates from cold-receptors in the tongue of the cat. *B* and *C* after HENSEL and BOMAN [27] and HENSEL and ZOTTERMAN [26], reproduced by permission.

Fig. 21, A, B.
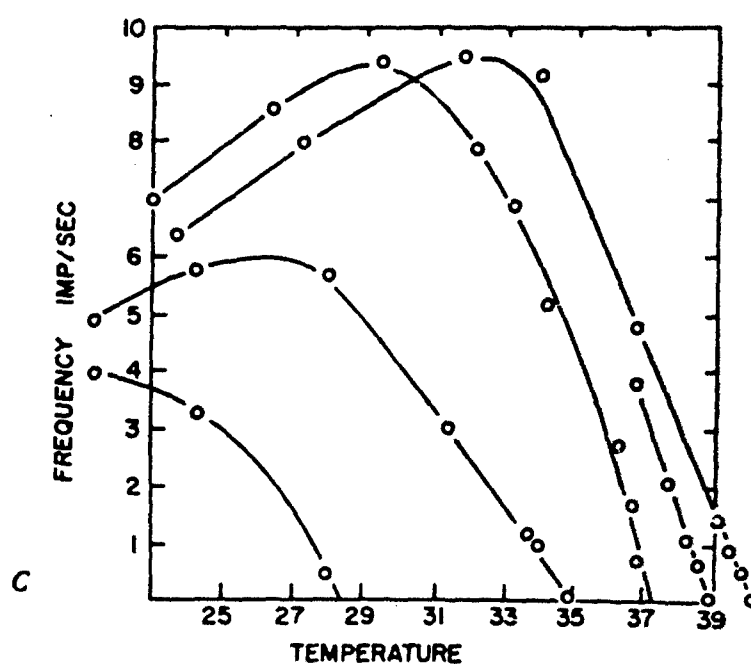
of an accidental nature under these widely varied conditions. The intended disruption of relation: was indeed successful as it appears from the plotted data in figure 21, *A* and 22, *A*. At first sight the graphs do not indicate any reproducible relationship of heat production as a response, either with the stimulus of skin temperature or with central temperature-reception.

Nevertheless, a quantitative resolution is obtained, when lines of equal cranial internal temperatures are drawn in figure 21, *B*, or lines of equal skin temperatures in figures 22, *B* and *C*. « Chemical » temperature regulation is explained as a result of two sensory temperature functions, cold-reception at the skin, and reception of central warmth. Cold-reception at the skin drives the response of metabolic heat production. When the internal cranial temperature is low (36.2 or less) this peripheral drive begins at a skin temperature threshold between 33 and 35.5° C. At a skin temperature of 20° C the cold-drive reaches a maximum, only to decline with further cooling of the skin. With rising cranial internal temperature a mounting depression of the metabolic responses is observed. At the « setpoint », where sweating would begin, the central warm-inhibition of the metabolic response becomes total. These mechanisms will appear more clearly after a review of present knowledge on centers and pathways involved.

CENTERS AND PATHWAYS

Between the cold-receptors of the skin and the main effector organs of chemical thermoregulation, namely, shivering muscles, afferent and efferent pathways have been demonstrated by numerous investigators beginning with the pioneering work of Isenschmidt and Krehl ([28]) and Isenschmidt and Schnitzler ([29]). Pertinent quotations from the literature were given in the references ([27, 28]) and more completely by Stuart in reference ([30]). From the latter we quote : « Shivering was consistently and repeatedly produced by electrical stimulation of the dorso-medial posterior hypothalamus... It was not produced by stimulation of any other region of the posterior hypothalamus... » « Conversely, shivering was abolished by destruction of the

Fig. 21. — *Chemical thermoregulation was explored in a series of tests extending over a period of two months, on one experimental subject.* The plotted measurements of oxygen consumption rates were obtained in water baths. By proper choice of bath temperatures and by preheating or pre-cooling in other baths, a wide variety of combinations between cranial internal and skin temperatures were obtained. This disruption of normal temperature-relations resulted in a seemingly senseless plot *(A)*. By drawing isotherms of tympanic temperature, 36.2 to 37.2°C, the plot is resolved *(B)*. Chimical thermoregulation is demonstrated to be a result of peripheral cold-drives and central warm-inhibition (See also figure 22).

dorso-medial region of the posterior hypothalamus. » In accordance with these recent findings and earlier ones, afferent and efferent pathways for thermoregulatory heat production are shown in figure 23, with synaptic connections in the Krehl-Isenschmidt-Center. The existence of such pathways is a minimum requirement to explain our findings ([26]) (fig. 17 to 22), that cold-receptor excitation is reflected quantitatively in levels and time-patterns of the metabolic heat production in the shivering muscles.
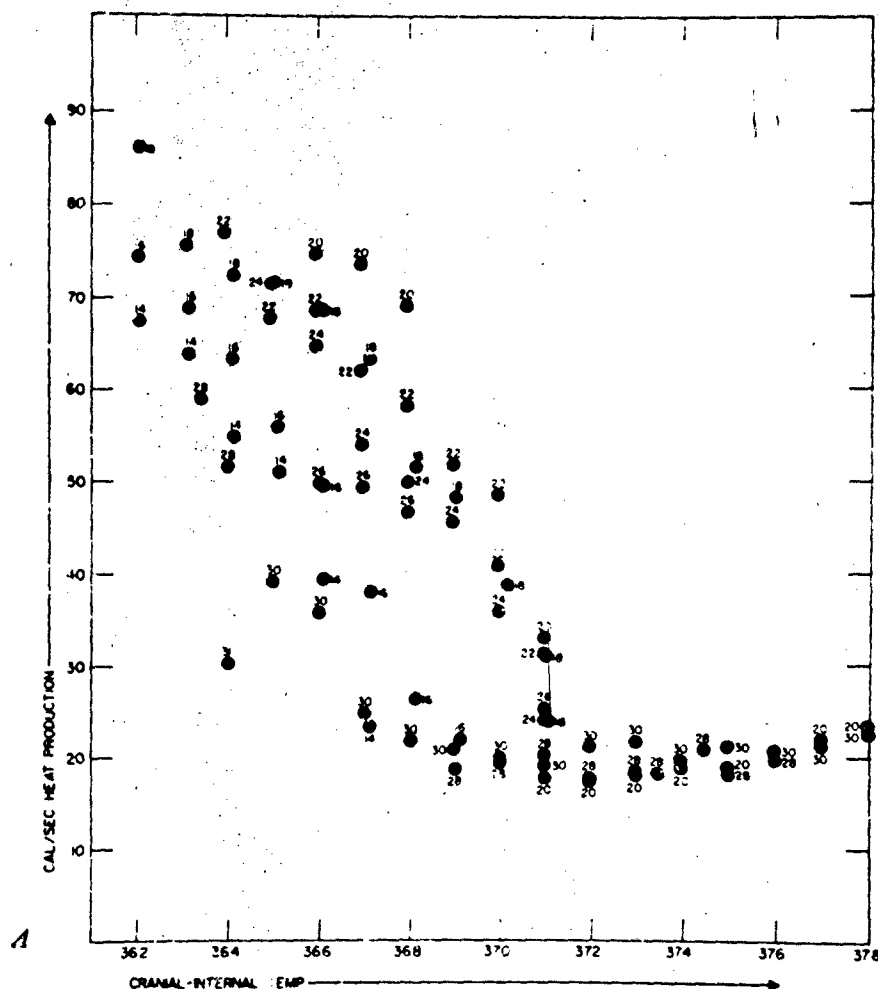
Fig. 22. — A seemingly senseless plot (A) is obtained when oxygen consumption-rates of figure 21 are plotted against tympanic temperatures. With skin-isotherms drawn in (B) and (C) chemical thermoregulation is resolved as an effect of cold-reception at the skin, and central warm-inhibition which becomes total at the « setpoint of the human thermostat ».

More, however, must be postulated from the calorimetric findings of figures 21 and 22, namely, that warm-impulses from a central sensor for temperature gain access to the shivering-pathways, for inhibition of the metabolic response (fig. 23). At 37.2° C central temperature and 20° C skin temperature, driving cold-impulses from the skin are abundant. Nevertheless, the response

Fig. 22 B.
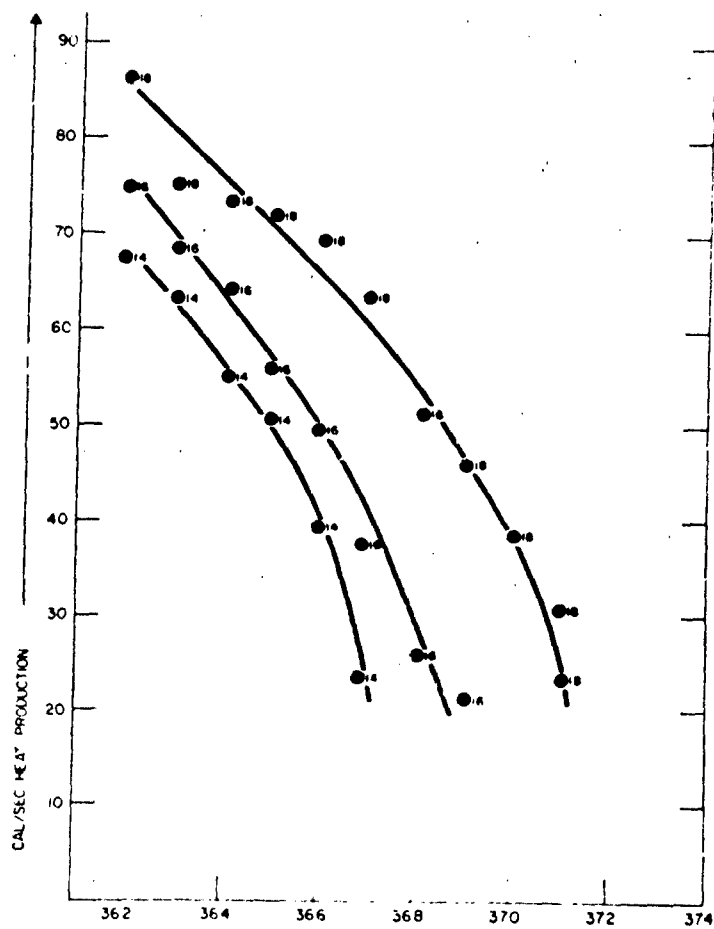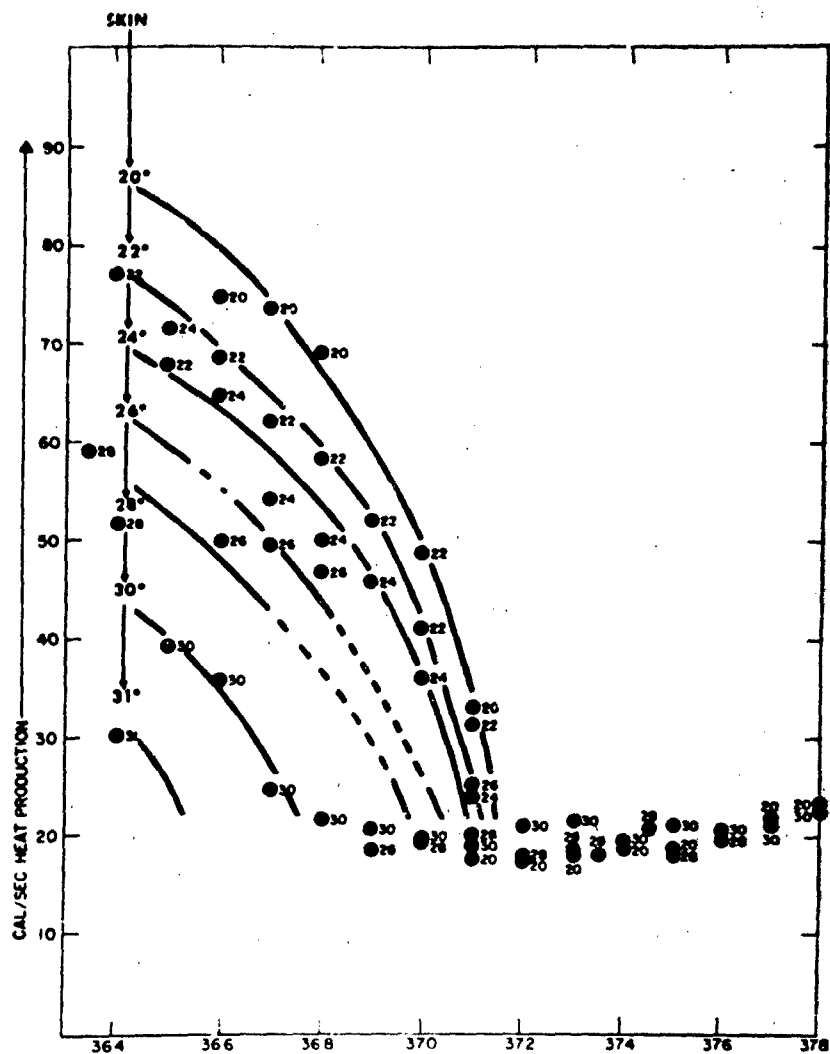
Fig. 22 C.

of shivering is completely suppressed by central counteraction (see fig. 21 and 22). The origin, pathway and target-area of central inhibitory warm-impulses have been demonstrated in the past repeatedly. In 1940, Hemingway *c.* al. ([31]) attempted to eliminate the shivering response by diathermic warming of the Krehl Isenschmidt-Center. These attempts were unsuccessful. However, when they heated the preoptic region, shivering was immediately abolished. While these authors placed their diathermy-electrodes at the lower surface of the brainstem, their experiments were successfully repeated by Freeman and
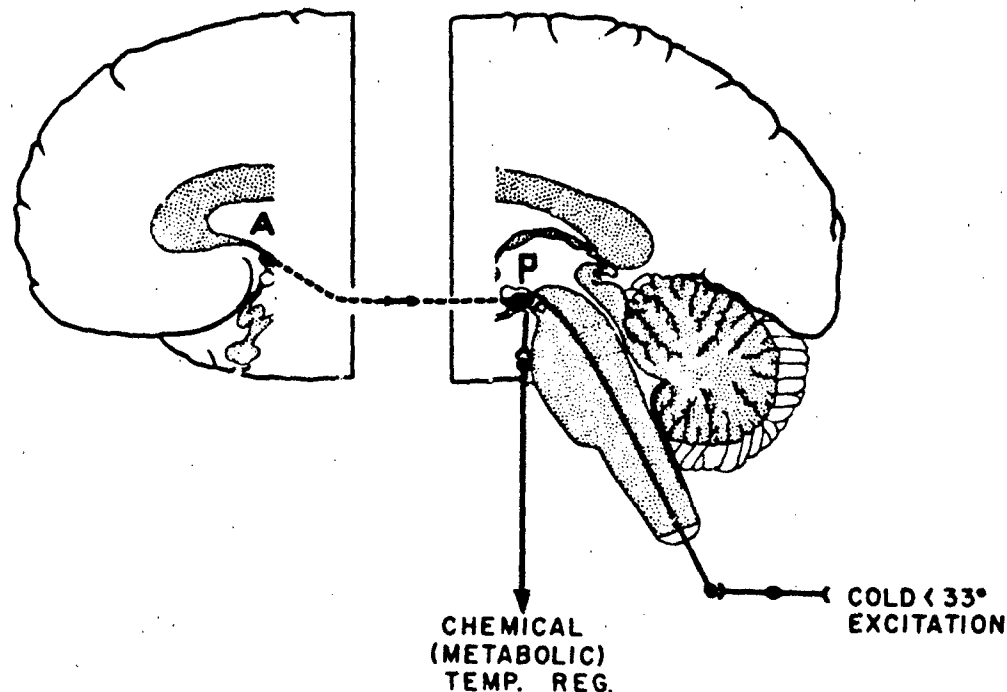
Fig. 23. — *The anatomical basis of the calorimetric observations of figures 21 and 22 are* (1) *an afferent pathway for cold-impulses from the skin, and* (2) *an efferent pathway for shivering, with a synaptic connection in the posterior hypothalamus (P), the Krehl Isenschmidt Center.* [28]. A third pathway (broken line) originating from the anterior hypothalamic heat loss center or « temperature-eye », *(A)* connects into the shivering network, for inhibition.

Davis ([32]) in 1959, with electrodes placed into the anterior and posterior thermo-regulatory centers. The results of both teams were identical. They are consistent with our findings, that central warm-reception restrains, and eventually blocks, the metabolic response to firing rates of cold-receptors of the skin. Pinkston, Bard and Rioch ([33]) found that the destruction of the preoptic region does not only leave intact, but even enhances the response of animals to cold by shivering. A pathway leading from the anterior to the posterior thermoregulatory center in the hypothalamus has been demonstrated by Hemingway in 1957 ([34]).

From a recent summary concerning anterior hypothalamic inhibition of shivering, by Stuart ([30]) we may quote : « Results of investigators... are in

agreement with respect to the localization of an anterior hypothalamic region whose activation suppresses shivering » ... and « Such results confirm the work of previous investigators who localized a « heat loss center » in the anterior hypothalamus. » Consistently then, the main result emerges, that two thermoregulatory centers are crucially important for chemical thermoregulation : 1° A posterior hypothalamic site for transmission of driving cold-impulses from the skin, 2° and an anterior hypothalamic site from which inhibitory warm-impulses originate (fig. 23).

These two centers are not « twins » of comparable organization and function. They differ in their. basic nature. The posterior center is temperature-blind. Its functions are merely synaptic. The anterior center performs differently, as a temperature-eye—generating its own sensory impulses,—a human thermostat with a driving action in physical, and a restraining action in chemical thermoregulation.

A terminal sensory organ by which two vital warm-receptive functions are exerted in the brainstem is not foreign to other functions and structures in the area. The anterior hypothalamus contains the matrix from which the retina is formed in the course of development. Behind the temperature-receptive center, osmoreceptors for water-content, and chemical receptors which create the sensations of hunger and satiation are located. More caudally, the stimuli of carbon dioxide or hydrogen ion concentration are received for the regulation of breathing.

Wide differences between animals and man, some of which were outlined above, must again be kept well in mind to understand that there is no contradiction between the findings here described for man, and findings in the dog by Chatonnet ([35]), Cabanac ([36]), Hammel ([37]). There is substantial evidence for central cold-reception in the dog. In man this mechanism does not make a major contribution to autonomic homeostasis in our own experience. Elsewhere, in experiments on 50 human subjects, cooled in water baths to rectal temperatures of 35° C and occasionally, 33° C, Beckman ([38]) has observed without exception the immediate cessation of shivering under a warm shower. When the wet skin was re-exposed to room air, shivering promptly recurred.

NEURONS AND THERMOREGULATION

While only measurements of temperatures and flows of heat permit to observe in thermoregulation the primary causes and the ultimate effects of action, knowledge on the intermediate events is required for full understanding. The thermoreceptor fields of thermoregulation are not safely identified, unless and until temperature-dependent firing rates of their sensory neurons have been demonstrated. For the peripheral receptor field Hensel and Zotterman ([26]) and Hensel and Boman ([27]) discovered the main electrical characteristics, before calorimetry permitted to find the connections between

skin temperatures as stimuli, and responses by metabolic action ([25]). For *central* thermoreception the sequence was reversed. By human calorimetry the main relations between stimuli and responses were found first ([9, 25]). A few years later, temperature-dependent firing rates of central neurons were discovered ([13]). We shall briefly discuss the remarkable consistency of results obtained with two independent approaches to thermoregulation : human calorimetry and electrophysiology of neurons.

The calorimetric experiments described above (fig. 18 and 22) require for their explanation the existence of skin cold-receptors which begin to fire, when temperature is lowered to 35° C or less (fig. 18, *A*). Maximal firing-rates are expected to be produced near 20° C, declining with a further fall in temperature. The receptors should respond to sudden cooling with overshooting impulse frequencies, and to sudden warming (fig. 19, *A*) with overshooting inhibition. These stringent requirements are met by the receptors which Hensel and Zotterman ([26]) have electrophysiologically investigated.

It would be most desirable to reach a similar degree of detailed understanding for the central thermosensory functions of man. From calorimetric evidence and subjective sensory experience (see below) absence or low significance of central cold-receptors would be expected. Absence of cold-receptors in the preoptic region has been observed in the cat by Nakayama et al. ([13]). In the study of Hardy et al. ([19]) cold-receptors were found in the dog to be present in relatively small numbers.

For man a further postulate from calorimetric measurements would be two different sets of warm-sensitive neurons, with different thresholds and maxima of firing rates : one for inhibitory warm-impulses with a lower threshold, and another set, for warm-impulses driving the responses of sweating and vasodilatation, from the setpoint upward. Indeed, two sets of neurons with different temperature-coefficients of their firing rates were found in the cat by Nakayama et al. ([13]). Not only the presence of thermosensitive units of different properties, but also species-differences in their characteristics have thus been demonstrated. A beginning has been made for a correlation of central impulses and responses. The presence of central cold-receptors in the dog is consistent with the demonstration of « *frisson central* » in the dog by Hammel ([37]) and by Chatonnet ([35]). The absence of central cold-receptors in the cat may have a parallel in man, where shivering ceases in the normal range of homeostasis, when driving cold-impulses from the skin are abolished.

For human physical and chemical thermoregulation the relations between central temperature and response-intensities are known (fig. 24). Firing rates are not, and probably never will be obtainable on man. In the expected permanent absence of human data it seems permissible to compare responses with central neuron firing rates that have been measured on animals by Nakayama et al. ([13]) and by Hardy et al. ([19]). Central warm-sensitive neurons appear to be far more sensitive than cutaneous cold-receptors. This compares well with the wider range of peripheral, and the narrow range of central temperature

reception. In caloric responses to receptor firing rates the central system appears again to be superior. The peripheral system, on the other hand, excels by its response to sudden changes. On primates, though not on man, it may become possible to find by calorimetry and electrophysiology the correlations between temperatures in the central receptor field, action potentials generated, and responses given in calories gained or lost to the central reception of warmth.
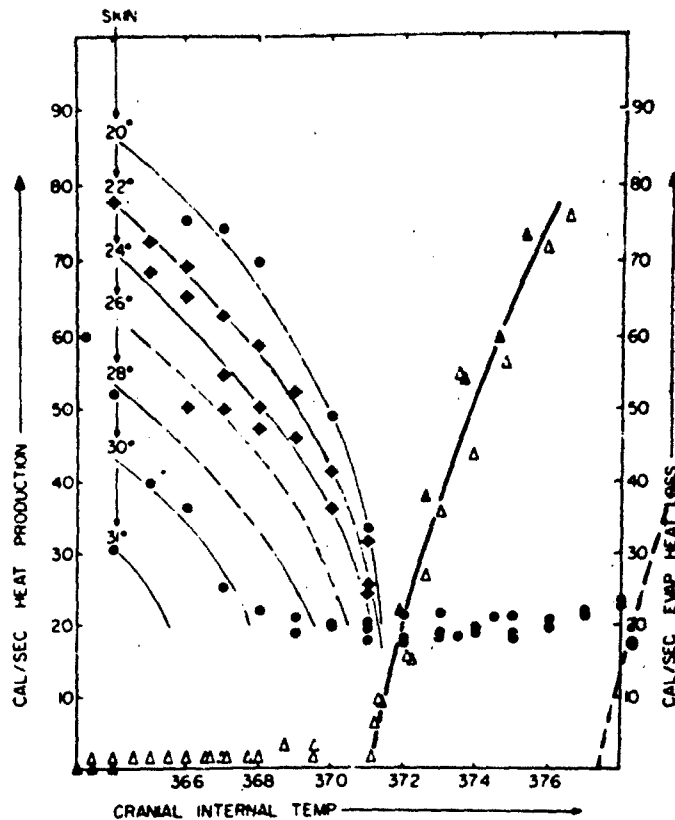
FIG. 24. — *The autonomic mechanisms of thermoregulation tend to maintain the thermal homeostasis of man close to a setpoint, which is reproducible within ±0.1°C (37.1°C in this particular individual).* The temperature-deviations to the right and left of the setpoint were introduced by thermal stress in hot environments (up to 45°C) or in cold baths (down to 14°C). The deviations (load-errors) elicited powerful responses of increased metabolic heat production (left from the setpoint) or evaporative heat loss by sweating (right from the setpoint). Through these responses gains or losses of heat were increased up to four times a normal metabolic rate at rest. Cranial internal (tympanic) temperatures were thereby maintained within limits of less than ± 1°C (frame of figure, range of autonomic homeostasis).

Physical thermoregulation is centrally elicited. Chemical thermoregulation originates from skin cold-reception. It is totally inhibited when central temperature reaches the setpoint. Forced gains or losses of more than four basal metabolic rates cannot be autonomically compensated. They must be averted by behavioral action.

The broken line shows a pathological setpoint-shift, caused by a minor dental irritation. Fever is outside the range presented in the figure.

SOME COMMON CHARACTERISTICS
OF PHYSIOLOGICAL AND MAN-MADE SERVOMECHANISMS

The source of physiological information is the physiological experiment. Considerations of analogy between physiological mechanisms and man-made devices, or experiments on mechanical or thermal models, cannot produce new physiological knowledge. Nevertheless, it is legitimate to compare certain experimentally observed characteristics that are common to man-made devices and to objects of human physiology. In our experiments on human thermoregulation, certain concepts of engineering have been observed experimentally as physiological realities.

On-off control. — In figures 10, *B*, 15, *B* and 24, it appears that below a distinct point on the scale of cranial internal temperature the response of sweating is « off » It is « on » at temperatures above that point. Therefore, to an observer with limited instead of continuous data, human thermoregulation might seem comparable to the on-off operation of a thermostat for home-use. In reality, the human system is more elaborate. It incorporates other highly important principles of automatic regulation.

Proportional control. — In figures 10 *B*, 15 *B* and 24, the corrective action, sweating, is practically proportional to the « load error signal », the deviation of cranial internal temperature from the setpoint, 36.85° C, 36.90° C, or 37.10° C, respectively, for these three individuals. This « proportional control » makes the human system comparable to advanced man-made servomechanisms, and superior to the conventional thermostat in a room, which is crude by comparison as a mechanism with mere « on-off » characteristics. A second example of central proportional control is the gradual release of the metabolic response to cold from central warm-inhibition (fig. 22, *C* and 24).

Rate control. — In figure 21, *B* the metabolic response to the excitation of skin cold-receptors demonstrates again proportional control : The response increases with decreasing levels of skin temperatures. Moreover, « rate-control » is superimposed on the proportional control, through the additional response to rate of change, and not only to the level of skin temperature (fig. 18 and 19). Thereby, the delaying effect of the thermal inertia of the body is circumvented. The response begins in an accentuated manner, even before the stimulus of cold reaches the controlling (hypothalamic) center. Both, the proportional and rate-control in this system tend to restore the norm by « negative feed-back, » negating a major deviation of internal temperature from the norm. (By contrast, warm-reception at the skin, a former hypothetical supposition for central sweating, would have the opposite result, by « positive feedback. »)

The superimposed rate-control exerted by cold-receptors of the skin has vital importance not only in autonomic, but also in behavioral thermoregulation as will be demonstrated later.

Setpoint. — In figures 10 B, 15 B and 24 there appears a distinguished point on the centigrade scale of central temperature, where the effector action by sweating begins or ceases, with increasing or decreasing temperature in each particular, healthy individual. In technical language « the position to which a control point setting mechanism is set in an automatic control, translated into units of the controlled variable » (36.85, 36.90 or 37.10° C in this example), is called the « set-point. » This term of engineering was first observed by us in 1959, as a physiological reality in thermoregulation. It is no doubt inherent in the molecular structure of the sensory cells by which the stimulus of cranial internal temperature is translated into nerve action, which results in the sweating response. The setpoint shows individual differences. Its location was found at different temperatures in the range between 36.6 and 37.1 on the seven U. S. Astronauts of the first generation (Mercury-project) (Table I) and on the Navy Corpsmen tested in this laboratory.

The setpoint is subject to shift. Between sleep and wakefulness Hammel [37] has found on dogs differences in the position of the setpoint. In fever, cranial temperature may rise excessively without a sweating response, which is interpreted as a shift of the setpoint to the right. Upon return of the setpoint toward the norm, while internal temperature remains temporarily elevated, an

Table 1. — Evaluation of the setpoint
of the human thermostat from sweating and from blood flow

Subject	Sweating Set Point, °C	Blood Flow Set Point, °C	Difference, °C
D. S.	36.48	36.40	+ 0.08
J. G.	—	26.45	—
V. G.	36.52	36.60	— 0.08
M. C.	36.60	—	—
W. D.	36.76	36.70	+ 0.06
M. S.	36.77	36.80	— 0.03
G. C.	36.80	36.93	— 0.13
A. S.	36.85	36.80	+ 0.05
Average	36.69	36.67	0.07

Individual differences in the setpoint of the human thermostat appear from measurements on six astronauts and their flight surgeon. Values were obtained by extrapolation to zero sweating and normal blood flowrate, from two measurements, environments 35° C and 45° C. The lowest setpoint observation was 36.5° C, the highest, 37.1°C (fig. 24).

outburst of sweating must be expected with the remission of fever. By cranial thermometry and with calorimetric observations more subtle influences of this kind can be demonstrated. In figure 24, one measurement of sweating came out exceedingly low, at elevated cranial temperature, as a result of a trivial disturbance : A few hours before this particular measurement was carried out, a root canal had been irritated by dental treatment of the experimental subject, who did not think it was worth being reported to those who conducted the test.

RANGE AND PRECISION
OF HUMAN AUTONOMIC THERMOREGULATION

Only by measurements of heat loss and heat production, and simultaneous measurements of stimuli of temperature may information be obtained on the ultimate performance and efficiency of the human thermoregulatory system. How close will the internal temperature be held to a predetermined standard under the influence of stresses of a given magnitude ? What are the maximal intensities of thermal stress which autonomic thermoregulation can outbalance ? Answers to questions of this kind are contained in a combined presentation of data measured on the same subject, in warm and in cold environments (fig. 24). To the right and to the left from the setpoint (37.1° C) at which both physical and chemical thermoregulation are inactive, losses or gains of heat are rising in proportion to the deviation from the setpoint, with a gradient of roughly 200 cal sec^{-1} deg^{-1}. In a different manner of speaking, the response is ten metabolic rates per 1° C (one basal metabolic rate ~20 cal/sec.) We might say that the regulatory strength of central physical regulation (sweating) is -10 BRM/$^\circ$C. It responds with an increase of 10% in basal heat loss to a deviation of 0.01° C from setpoint-temperature. The deviations from the norm which the system permits are small indeed : under an additional heating or cooling-load of a full metabolic rate cranial internal temperature rises or falls only by 0.1° C. For, the regulatory power of the central release of metabolic action from warm-inhibition is equally strong : $+10$ BMR/$^\circ$C. This mechanism depends, however, on the delivery of cold-impulses from the skin as a presupposition. The driving power of the cold-receptors of the skin is found in figure 13 B, from the gradient of any of the family of curves as it rises to the left from the level of basal metabolic rate : $+0.2$ BMR/$^\circ$C. The peripheral, driving component of the system covers a wide range of skin temperatures. It is accordingly, less sensitive to temperature than the central (inhibiting) function, which operates over a very narrow range of temperature below the setpoint. Strong by comparison ($+2.0$ BMR/$^\circ$C) is the anti-homeostatic inhibition of sweating during cold-reception at the skin, that prevents the simultaneous activation of physical and chemical thermoregulation.

Such antagonism, if it occurred, would be wasteful and disadvantageous for various reasons. The blocking mechanism (fig. 10) has proportional characteristics. It is not an all-or-nothing response.

During forced gain of heat in the amount of four times a basal metabolic rate (20 cal/sec) an upward deviation of 0.4° C from the setpoint must be expected. It must be accepted as the « load error » that is required to drive the response. For chemical thermoregulation it is not possible to make a similar direct prediction. An important difference between defenses against overheating or cooling deserves attention. In figure 16, at elevated temperatures, the sweating rates were fully compensating the gains and production of heat. The subject was in balanced condition with an elevated, but steady temperature in the range observed. In the cool baths, where the metabolic responses to cutaneous and central temperatures were measured as shown in the figure, heat loss (not measured) exceeded heat production, as internal temperatures fell continuously in consequence of the cold-stress. Unlike the sweating response, which compensates the gains, the metabolic response is not intense enough to offset the losses. Moreover, at moderately low skin temperatures there is no immediate metabolic action, when central temperature falls below the setpoint (see leftward curves in fig. 22, C and 24). Because of these deficiencies, shivering and metabolic heat production cannot by themselves maintain the homeostasis of man in cold environment. Unlike sweating, shivering is an emergency function, not a regular activity. The existing gap is bridged by « behavioral » thermoregulation in cold environment, as will be demonstrated later.

Whereas the power of thermoregulatory mechanisms is best described as a relation between load-error and response, the precision is best described as the reproducibility of the setpoint. From figures 10 B, 15 B and 24, setpoint-reproductibility is estimated at ±0.1° C or better, provided that the setpoint is determined during daytime, as the experiments were carried out during working hours, over periods of weeks or months to obtain the data as shown.

Homeostasis, known and unknown factors. — When ultimate aims of thermoregulatory research are compared with present experimental data, certain questions appear to be answered, others are open. While calorimetric information on the responses is comprehensive (because it covers total, not partial or local losses or gains of heat), the exploration of the stimuli is less complete or final. Our investigation has differentiated only between cutaneous and central temperature-reception. Effects of central temperature were attributed to stimulation of the one internal sensor that has been established beyond doubt with the methods of experimental neurosurgery and electrophysiology. Yet, stimulating or inhibiting effects from locations other than the skin or the anterior hypothalamus cannot be excluded with certainty at this time. If there existed thermoreceptors in the core of the body, in the respiratory, visceral or vascular systems, it would be important to know their location and to evaluate their possible contribution to the responses observed. Sensory temperature reception in the upper respiratory tract and in the area of the fifth cranial nerve may deserve special attention as a possible origin of thermoregulatory impulses in warm or cold.

After a search in the upper intestinal tract with negative results, Thauer ([39]) reported metabolic responses to a perfusion of the vertebral canal with chilled liquids in the dog. However, to produce a shivering-response equivalent to one basal metabolic rate, a perfusion-temperature approximately 30° C below normal was required in these experiments. For comparison, in our experiments on man (fig. 10, 22 and 24) responses of one basal metabolic rate were elicited by temperature differences 300 times smaller; variations of only 0.1° C in central temperature. Therefore, in the range of human thermal homeostasis which is maintained within ±1° C as shown in figure 24, the effects which Thauer observed with violent cold-stimulation of the spinal cord could not make a measurable contribution. In physical thermoregulation direct effects of temperature upon blood vessels, axon reflexes, and contralateral vascular reflexes play their rôles (see fig. 16 B). Direct effects of skin temperature upon sweat gland activity, and « non-thermal effects » of exercise upon sweating have been observed elsewhere.

Adaptation of sweating (and perhaps, sweat glands) has been demonstrated beyond doubt.

Particular attention has been given to « reflex sweating. » With the iodine-starch paper technique (a highly sensitive, non-quantitative test) Randall ([40]) observed an elicitation of contralateral, reflex sweating in man. Randall applied temperature-stimuli which merge a « hot sensation into one of severe pain, » by immersion of limbs with tourniquets in water of 47° C. (For comparison, skin temperatures in the hottest environments, where human thermoregulation operates with homeostatic success, were always below 38° C in our tests.)

Like the observations of Thauer with cold-stimulation of the spinal cord so the observations of reflex sweating by Randall were made under excessive thermal stimulations. These were outside the range in which the thermal homeostasis of man is maintained as demonstrated in figure 24 and others. To physical thermoregulation as described in these graphs, the effect observed by Randall cannot have made a measurable contribution.

Chemical, not only neural events are known to affect the production of heat and thereby the internal temperature and thermal homeostasis. Equilibria as well as rates of biochemical reactions in metabolism are temperature-dependent. Their direct relation to temperature is bound to result in homeostatic or in anti-homeostatic effects. Moreover, hormonal mechanisms are known to come into play in prolonged exposures to thermal stress. Long-term adaptations of metabolism have been demonstrated to support chemical thermoregulation. These various factors including the phenomenon of hibernation are being studied intensely in numerous laboratories.

The unsolved questions notwithstanding, present experimental data summarized in figure 24 explain the phenomenon that was the starting point of this investigation : The near-invariance of body temperature in man under a wide variety of environmental conditions. The milieu intérieur is constant, while the environmental temperature changes. Internal temperature is maintained near the setpoint, because minute deviations to the right or left are counteracted by responses of unusual power.

BEHAVIORAL THERMOREGULATION

In man and animals internal temperature is guarded by two, not only one—homeostatic systems : Behavioral and autonomic control. Thermal behavior is effective against stresses of enormous range. It is, however, not capable of any degree of regulatory precision. The autonomic thermostatic system described with figure 24, provides the almost unbelievable precision of control. Conversely, the autonomic system has a limited range. With increasing thermal stresses and deviations from the setpoint a flattening of the response curves is observed. The efficiency of the regulatory mechanism decreases with further rising load-errors and with mounting demands on the limited capacity of exhaustible effector mechanisms. It is a matter of choice, how far one should propose to strain the physiological defenses with diminishing returns, where one should discontinue to rely on their protection in various environments and activities. It would appear from figure 24, that gains or losses not exceeding four metabolic rates are acceptable, if only for short periods, although higher sweating rates have been observed under extreme environmental conditions. Diminishing returns would recommend for man to use for his further protection as early as possible the almost unlimited resources available to him from behavior and from that inventive extension of human intelligent behavior, which is called *technology*.

In autonomic thermoregulation, the reception of temperature is unconscious. Autonomic responses are unwillful. Behavioral thermoregulation operates by voluntary actions. It is based upon the conscious perception of temperature. On the effector side, the apparatus employed is non-specific. It is the muscular system, much like in any other behavioral mechanism. Only the sensory apparatus of thermal behavior is temperature-specific. The main behavioral drives, like in autonomic thermoregulation, are the peripheral reception of cold and a central reception of warmth. This will be demonstrated in the following two chapters.

Subjective sensation of cold. — Human subjects are capable of reproducing with a fair accuracy, the threshold of beginning cold-sensation at the skin, when skin temperature over the entire body is lowered gradually in a bath at a rate of $1°C/hr$. Does the threshold of cold-sensation ($\sim 35°C$) differ at different central temperatures, as might well be expected from experience with the dramatic inhibition of peripheral cold-drives for metabolic action by central warming (fig. 22 B) ? In figure 25, thresholds are plotted against internal cranial temperatures for both, the unconscious metabolic response to cold and the conscious sensation of cold. Obviously, the conscious sensation of cold at its threshold value is not aggravated by low central temperature, nor is it alleviated by central warm-reception. (The apparent minor downward shift of the threshold with rising central temperature is an artifact explained in the legend.) Nevertheless, there is a conscious equivalent to internal cooling : When low internal temperature abolishes the central warm-inhibition and releases the response of shivering, the conscious

cold-sensation, otherwise unchanged, assumes an alarming quality. This change in subjective connotation is explained as a perception of the strange, involuntary movements combined with cold-perception from the skin, rather than as a perception of low internal temperature as such. The non-existence of unpleasant sensations from low internal temperature is readily demonstrated as follows : When transferred into an indifferent or moderately warm water bath, after pre-cooling and intense shivering in a cold bath, human subjects experience immediately a most delightful subjective state of thermal
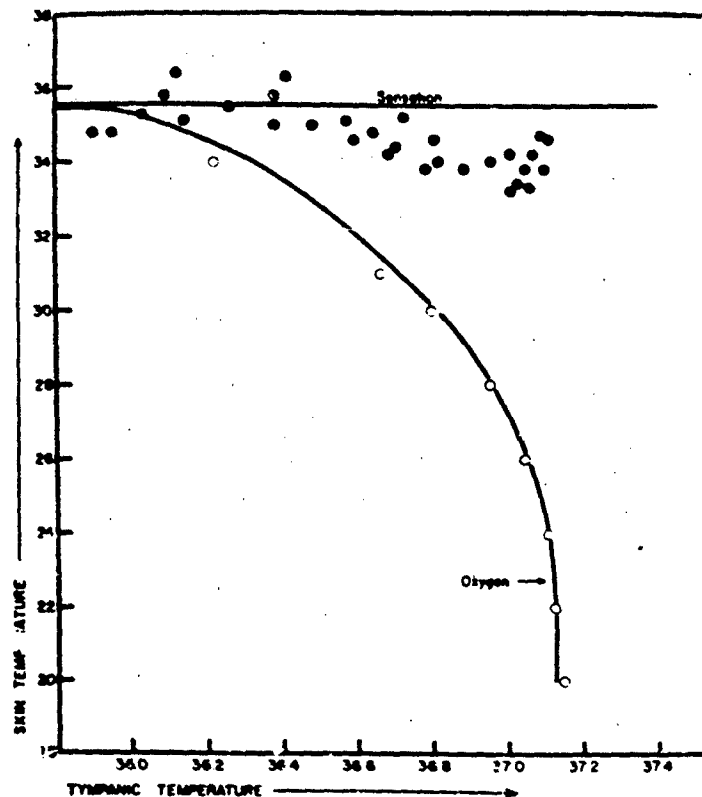
Fig. 25.

The conscious sensation of cold (black dots indicating receptor threshold temperatures) *is compared with the unconscious metabolic response to skin cold-reception* (rings indicating skin temperatures at which the metabolic response is released from central inhibition). The dramatic inhibition of the metabolic response by central warm-reception has no parallel in the conscious cold-sensation, although the extrapolated receptor-threshold are identical. The slight apparent lowering of the threshold of sensation with rising central temperature is an artifact : instead of the actual, subsurface receptor temperatures that should have been measured, skin surface temperatures in water were measured and plotted. When internal temperature is elevated (at right), the actual subsurface receptor temperatures (real thresholds) are higher than the surface temperatures as measured and plotted (observed apparent thresholds)

comfort, at very low internal temperatures. In the absence of both, driving warm-impulses of central origin, and driving cold-impulses from the periphery, a state of perfect comfort and tranquility is enjoyed. Quite often, subjects fell asleep under these pleasant conditions in our laboratory.

The contrast between metabolic action, which is dramatically inhibited by central warming, and the conscious sensation of cold from the skin, which is not inhibited at all, is striking. This lack of central warm-inhibition in behavioral thermoregulation has extraordinary importance for the survival and performance of man in cold environments. Because of serious deficiencies in chemical thermoregulation discussed above, homeostasis in cold could not be maintained without the immediate and overshooting warning of cold from

the skin; it could not be preserved without behavioral reactions. Internal temperature would drift unnoticed, until the response would come too late, when both internal and skin temperature have fallen low. Even then, the shivering response would be insufficient to replace the heat withdrawn from the body by the impact of cold on the skin. Therefore, in cold environment man depends on behavior for survival. He continues to be active and does not sleep unless from exhaustion, as long as his skin is cold. If he goes to sleep, he is threatened with hypothermia. Normally the cold-warning from the skin, accentuated by the response to rate of change (rate-control), prevents that internal temperature falls substantially below the setpoint. During the night, half consciously, a blanket is drawn over an exposed shoulder. Soon thereafter, incipient sweating may be observed and produce an opposite reaction in the sleeper. By this means, temperature is held to the setpoint, through interaction of the behavioral response to peripheral cooling with the autonomic response to central warmth by sweating.

Subjective sensation of warmth. — As a warning signal against over-heating, warm-reception at the skin cannot play a major part for an obvious reason : It is not, like cold-reception, an unpleasant sensation, until the pain threshold is reached, far out of the physiological range of environmental stress. The unpleasant conscious sensation of being overheated is predomi-nantly of central origin. This can be readily demonstrated on man in a bath of 38.5° C (which is warmer than the highest skin temperatures attained under the stress of environments of 45-50° C). With the same high skin temperature, a subject can feel either perfectly comfortable (at low internal cranial tempe-rature), or be in severe distress (at high internal cranial temperature). Entering the 38.5° C bath with a low internal cranial temperature, the subject feels comfortable and pleased, and not even warm. With increasing cranial internal temperature the condition is first described as pleasantly warm rather than cool or indifferent. With further increasing cranial temperature the sensation becomes gradually uncomfortable. At last, an almost unbearable urge to leave the warm bath arises (fig. 26). This warning, reportedly, is heeded likewise by Sauna-bathers. Few or no heatstroke-casualties have been reported to our knowledge in connection with the Finnish bath, inspite of its wide usage.

This central sensation of warmth, when fully developed is strong. It is however, vague and inaccurate in comparison with autonomic responses, and late in arrival. While the conscious sensation of cold usually precedes the autonomic response of shivering, the autonomic response of sweating usually precedes the conscious sensation of being overheated.

Internal warm-sensation is swiftly and effectively quenched by excitation of the cold-receptors of the skin, which under these conditions is felt as a relief, an invigorating sensation.

The central site from which the unpleasant sensation of warmth arises is known at least indirectly, from animal experiments by Hardy ([41]). « Basking behavior » is the typical behavioral response of dogs to artificial local warming of the preoptic region.

The dominating presence of central warm-reception in man, for conscious sensation as well as for autonomic control, is a fact of major importance. It contrasts sharply with the inferior or non-existent rôles in man (not animals) of central conscious cold-sensation and central cold-drives for metabolic action. The subjective findings, so readily demonstrable in a bath, at least in a qualitative manner, make a substantial participation of cold-receptors of the human brain in behavioral regulation unlikely. Subjective central warm-sensation, on the other hand, is demonstrated beyond doubt on animals and man (fig. 26).
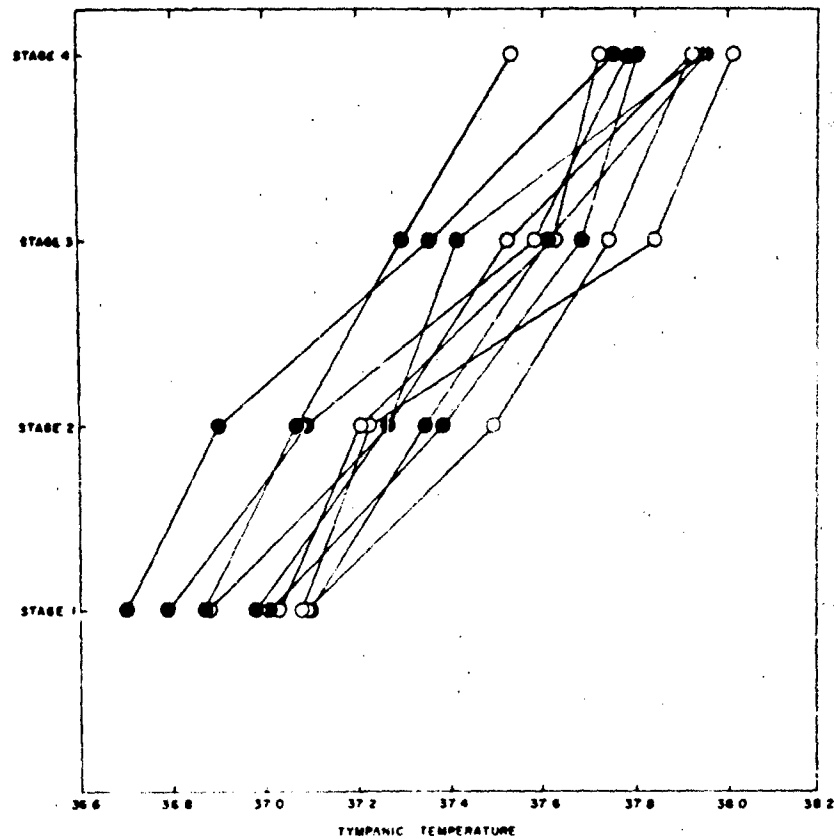
FIG. 26. — *Conscious central warn-reception is demonstrated by subjective observation of four stages of warm-sensation in a warm water bath of constant temperature, 38.5 C* (a high skin temperature, characteristic of 45 to 50°C environments in air). At low internal (tympanic) temperature, in stage 1, the subject feels comfortable and indifferent. At slightly elevated central temperature the subject feels comfortable and warm rather than cool (stage 2). Moderately unpleasant warm-sensation characterizes stage 3. In stage 4, the warm-sensation is intense and the subject wants to leave the bath.

SOME ASPECTS OF THERMOREGULATORY TECHNOLOGY

Stimulated by the unpleasant drives of peripheral cold or central warm-reception, or merely by the pleasant or unpleasant memories of thermal comfort or discomfort in his past, man has created a variety of useful thermal devices. Unlike mammals and birds man is not burdened with a permanent fur or feathers. Instead he fabricates and dons or sheds at will, a great variety of garments of his own design. To isolate himself against adverse

climatic influences man builds more elaborate shelters than animals do. He also designs for thermal protection and isolation his craft for travel on land, at sea, in air and space. By locomotion of extraordinary range and speed man changes swiftly from one environment to another. Such travel is often meant for climatic relief or pleasure. In other instances man moves with special craft into the most adverse situations with strenuous demands on his ingenuity for thermal survival.

When locomotion and insulation become insufficient as means of protection, energy from external sources is harnessed to heat shelters, working spaces and vehicles. The first important step of such technology was, of course, the invention of fire. A new dimension was opened by refrigeration, a late achievement of physics in the 19th century. Subsequent improvements were servomechanisms for temperature-regulation, with early contributions from the laboratory of Arsène d'Arsonval. Later the thermostat in the home became a standard item.

When the environment of man shrinks into a space-suit, the environmental thermostat becomes insufficient. It does not properly account for drastic variations of internal heat production. A further step in thermal technology is then required : Heating or cooling of the suit must be designed to regulate not suit-temperature proper, but the internal temperature of man himself. Cooling must take place, when cranial internal temperature exceeds the physiological setpoint. Warming must occur, when internal temperature falls below the setpoint. To this effect a cranial thermometer is required to replace the environmental thermostat. However, the secure positioning of such a device would be too critical, when it is used not only for measurement but also for automatic control. Therefore, we propose to replace man-made internal thermometers with the human sensor proper. This can be done by monitoring with man-made devices the physiological response to cranial internal temperature—the rate of sweating—not cranial temperature directly. When cold-inhibition from the skin is absent, incipient, barely perceptible, low-rate sweating indicates that the internal human sensor operates slightly above the setpoint, in the range of optimal comfort and performance. A system as described would indirectly regulate the cranial internal temperature, and maintain temperature at the individual setpoint by way of the relation between cranial internal temperature and the response of sweating (fig. 10 B. 15 B and 24). This would be a first servomechanism and control-loop, in which an unconscious sensory receptor of man cooperates with man-made effectors, devices for heating or cooling. An experimental system of this kind is under consideration in our laboratory.

CLINICAL APPLICATIONS
OF MODERN CONCEPTS AND METHODS

On this occasion honoring Claude Bernard, the physician, it seems appropriate to conclude with the importance of thermoregulation, not for the conquest of remote spaces, but for the missions of clinical medicine, diagnosis and treatment. One practical application of the concept of homoestasis des-
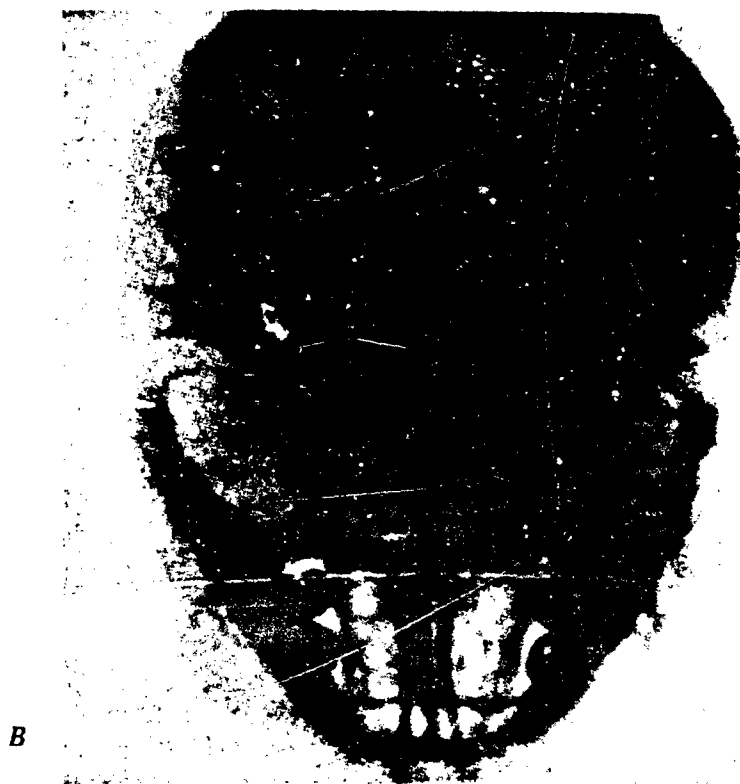
Fig. 27, *A* and *B*. — *X rays show in two projections a bag, filling and outlining the upper retropharyngeal cavity with contrast-medium*. Two catheters employed for perfusion with hot (50°C) or cold (0°C) water are visible. In *B* the rear edge of the nasal septum is seen as it partly bisects the bag. A thermocouple is discernible in the anterior ethmoidal region. Only limited changes of cranial temperature could be produced with this device. (Subject T. H. B.)

cribed in this paper, would be the usurpation of physiological control through selective artificial heating or cooling of the human thermostat. Preliminary attempts at this objective have been made in our laboratory. Figure 27 shows in two projections a bag for perfusion of the upper retropharyngeal cavity with water of 0° C or 50° C, respectively. Conductive warming or cooling accomplished in this manner was found to be inadequate for clinical applications. More efficient was heating of the carotid arteries by microwave-diathermia of 12.2 cm wavelength, which elicited sweating promptly (fig. 28). Focal, electromagnetic heating of the preoptic region was under consideration.
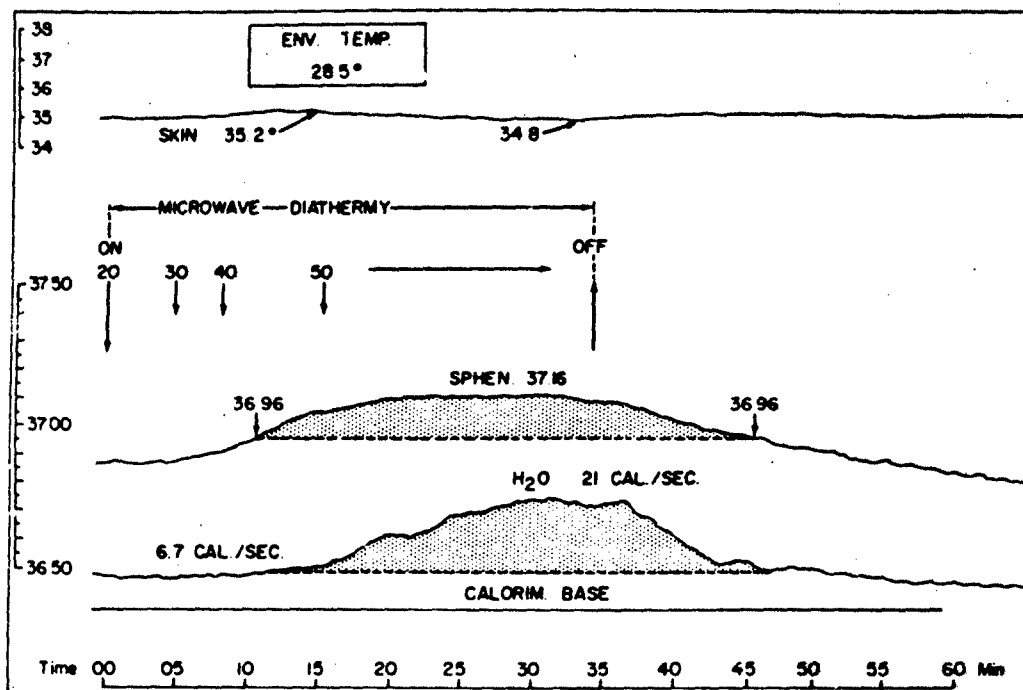
Fig. 28. — *Microwave-diathermy of both sides of the neck leads to a substantial increase of cranial temperature, measured at the anterior wall of the sphenoid sinus.* When the setpoint, 36,96°C, is reached, sweating is elicited and continues until cranial temperature returns to normal. (Subject T. H. B.)

It is, however, judged to be too hazardous in the present state of the art. Research into these possibilities should, nevertheless, be continued for the following reason : Selective warming of the preoptic region during the induction of hypothermia for surgery would eliminate without drugs the defenses of chemical thermoregulation. The well known delay of the hypothermic procedure and an exhaustion of metabolic or circulatory reserves of the patient could thus be avoided. When general hypothermia is accomplished, cerebral hypothermia could be promptly induced, by discontinuation of the local artificial heating.

While such an artificial « anti-homeostasis » is in the early stage of research, the new method of ear thermometry is ready for general introduction after technical developments of small and convenient read-out devices and soft, disposable probes. Some investigators have considered the tenderness of the

tympanic membrane an obstacle to patient-acceptance [Cooper [42]]. This can be circumvented by one of two ways, either : a) measurement of air or wall temperature in the auditory canal instead of a direct contact-measurement with the tympanic membrane ([42, 43]) (This method is of lower quality, but still better than available classical methods, rectal and oral thermometry); or b) development of special disposable receivers, to sense tympanic temperature over a short distance. This second and superior modification has been successfully pursued by Wortz ([44]). A further refinement of clinical and physiological thermometry is possible with measurements or recordings of the setpoint and its variations, rather than temperature as such. For this exten-sion, simultaneous observations of thermoregulatory responses are required. The time-honored method of rectal thermometry, so visibly inadequate for physiological investigation, has rendered a fair service to the physician over a period of more than 100 years. Pathological deviations are much wider than physiological fluctuations of temperature. Observations like those of figures 11 A-D, suggest, however, that subtle details of typical temperature patterns and important maxima or minima must have remained unrecorded in a long history of medical thermometry. Aside from typical temperature patterns of infectious diseases other, more subtle changes such as responses to treatments, recovery from surgical or other trauma, hormonal or mental dis-turbances and physiological rhythms deserve renewed and increasing attention and study. Adducci ([45]) was first to apply our method to the detection of ovu-lation for purposes of birth control. Piironen ([46]) has used tympanic thermo-metry in the field of thermal stress. Guidry and McDowell ([47]) have made first important applications to veterinary physiology. In astronautics, ear thermometry is now an accepted procedure.

SYNOPSIS

In further attempts to understand the thermal homeostasis of man new methods—gradient layer calorimetry and cranial thermometry—were deve-loped and utilized. Gradient calorimetry and indirect calorimetry permitted to measure at low inertia, losses or gains of heat, the effects or responses in thermoregulation. Cranial and skin thermometry permitted to measure directly, physical causes or stimuli near the sites of reception. Quantita-tive, reproducible and physiologically meaningful relations between stimuli and responses were observed. The stimuli are subtle, the responses are power-ful by comparison. « Physical » thermoregulation was found to be elicited by central warm-reception. « Chemical » thermoregulation was found to originate from cold-reception at the skin. Yet, it is ultimately controlled like physical thermoregulation by central warm-reception, with an inhibitory function. ——

The findings of gradient calorimetry and indirect calorimetry combined with cranial thermometry are consistent with the classical discoveries concer-ning centers and pathways of thermoregulation. They are consistent with the temperature-dependent patterns of firing-rates in peripheral or central, cold-or warm-receptive neurons as observed in other laboratories.

Power and precision, thresholds, ranges and limitations of the autonomic mechanisms were described. A comparison of the calorimetric findings with well-known concepts of engineering demonstrated basic similarities between man and his technical devices. Servomechanisms and negative feedback, load-errors and the setpoint, on-off, proportional and rate-control were found to be common to physiological mechanisms in man, and man-made control systems. Applications of the experimental findings and cranial thermometry-techniques are briefly discussed. /.

An investigation of behavioral thermoregulation revealed, that the conscious, sensory information on which the willful psychomotor responses depend, arises from peripheral cold-and central warm-reception, much like in autonomic thermoregulation. Unlike the *metabolic* response to cold, however, the *behavioral* response to cold is *not* subject to central warm-inhibition.

In the broad range of thermal stress which it may cover, behavioral thermoregulation is superior to autonomic control. Its range is unlimited for most practical purposes, when technology extends the resources of intelligent thermal behavior with external supply of energy. Nevertheless, only the autonomic system can provide the almost incredible precision and reproductibility of the thermal homeostasis of man.

Supreme autonomic control of thermal homeostasis by the nervous system was envisioned by Claude Bernard. His views were substantiated in numerous classical investigations during this first century following his main work. It was our limited task to demonstrate experimentally, how homeostatic control is enforced by the central nervous system, as human body temperature is held close to an absolute setpoint by means of a human thermostat, a terminal sensory organ for warm-reception in central position.

REFERENCES

(1) LAVOISIER (A.) : Mémoire sur la Chaleur, 1777, in *Œuvres de Lavoisier*, tome II, p. 1, Paris, 1862.

(2) D'ARSONVAL (A.) : Recherches de calorimétrie. *Journ. Anat. et Physiol.*, 1886, **22**, 8.

(3) RICHET (CHARLES M.) : Régulation de la température. *Physiologie*, 1893, **14**, 431.

(4) RICHET (CHARLES M.) : *Le frisson. Physiologie*, 1895, **39**, 1.

(5) RICHET (CHARLES M.) : De l'influence des lésions du cerveau sur la température. *C. R. Acad. des Sci.*, 1884, **98**, 295.

(6) BENZINGER (T. H.) et KITZINGER (C.) : Direct calorimetry by means of the gradient principle. *Rev. of Scient. Instr.*, 1949, **20**, 849.

(7) RUBNER (M.) : Ein Calorimeter für physiologische und hygienische Zwecke. *Zeitsch. für Biol. (München)*, 1888, ‾ 400.

(8) BENZINGER (T. H.) et KITZINGER (C.) : Gradient layer calorimetry and human calorimetry. *Temperature. Its measurement and control in science and industry*, 1963, **3**, 87.

(9) BENZINGER (T. H.) : On physical heat regulation and the sense of temperature in man. *Proc. Natl. Acad. of Sc.*, 1959, **3**, 645.

(10) BENZINGER (T. H.) and TAYLOR (G. W.) : Cranial measurements of internal temperature in man. *Temperature. Its Measurement and control in science and industry*, 1963, **3**, 111.

(11) Benzinger (T. H.) : The thermal homeostasis of man. *Symp. Soc. Exp. Biol.*, 1964, **18**, 49.

(12) Beaumont (W.) and Bullard (Van L. W.) : Sweating : Its rapid response to muscular work. *Science*, 1963, **141**, 643.

(13) Nakayama (T.) : Thermal stimulation of electric activity of single units of the preoptic region. *Am. J. of Physiol.*, 1963, **204**, 1122.

(14) Belding (H. S.) and Hertig (B. A.) : Sweating and body temperature following abrupt changes in environmental temperature. *J. Appl. Physiol.*, 1962, **17**, 103.

(15) Minard (D.) : Sweat rate during work and rest at elevated internal temperatures. *Fed. Proc.*, 1963, **22**, 177.

(16) Bullard (Robert W.) and Beaumont (W. Van) : Sweating, direct influence of skin temperature. *Science*, March 1965, **147**.

(17) Benzinger (T. H.) : The diminution of thermoregulatory sweating during cold-reception at the skin. *Proc. Natl. Acad. of Sc.*, 1961, **47**, 1683.

(18) Villablanca (J.) and Myers (R. D.) : Fever produced by microinjection of typhoid vaccine into hypothalamus of cats. *Am. J. Physiol.*, 1965, **208**, 703.

(19) Hardy (J. D.) et al. : Temperature-sensitive neurones in the dog's hypothalamus. *J. Physiol.*, 1964, **175**, 242.

(20) Euler (C. von) : *J. Cellular Comp. Physiol.*, 1950, **36**, 333.

(21) Barbour (H. J.) : *Arch. Exp. Path. Pharm.*, 1912, **19**, 1.

(22) Andersson and Persson (N.) : Pronounced hypothermia elicited by prolonged stimulation of the « Heat loss centre » in unanaesthetized goats ». *Acta Physiol. Scand.*, 1957, **41**, 277.

(23) Magoun (H. W.) et al. : *J. Neurophysiol.*, 1938, **1**, 101.

(24) Benzinger (T. H.) and Kitzinger (C.) : The human thermostat. *Temperature. Its measurement and control in science and industry*, 1963, **3**, 637.

(25) Benzinger (T. H.), Pratt (A. W.) and Kitzinger (C.) : The thermostatic control of human metabolic heat production. *Proc. Natl. Acad. of Sc.*, 1961, **47**, 730.

(26) Hensel (H.) and Zotterman (Y.) : *Acta Physiol. Scand.*, 1951, **23**, 291.

(27) Hensel (H.) and Boman (K.) : Afferent impulses in cutaneous sensory nerves in human subjects. *J. Neurophysiol.*, 1960, **23**, 564.

(28) Isenschmidt (R.) and Krehl (L.) : *Arch. Exptl. Pathol. Pharmakol.*, 1912, **70**, 109.

(29) Isenschmidt (R.) and Schnitzler (W.) : *Arch. Exptl. Pathol. Pharmakol.*, 1914, **76**, 202.

(30) Stuart (D. G.) : Nervous control of shivering. A Review. *Technical document report*, AAL-TDR, 1962, **62**, 11.

(31) Hemingway (A.) et al. : *J. Neurophysiol.*, 1940, **3**, 329.

(32) Freeman (W. J.) and Davis (D. D.) : *Am. J. Physiol.*, 1959, **197**, 145.

(33) Pinkston (J. O.) et al. : *Am. J. Physiol.*, 1934, **109**, 515.

(34) Hemingway (A.) : *Alaskan air command technical Note.* AAL-TN, 1957, **40**.

(35) Chatonnet (J.) and Tanche (M.) : Dissociation du frisson central et du frisson réflexe chez le chien à moelle détruite. *J. Physiol., Paris*, 1956, **48**, 439.

(36) Cabanac (M.) : Démonstration expérimentale de l'existence dans *l'hypothalamus d'une sensibilité au froid*, Thèse méd., Lyon, 1961.

(37) Hammel (T.) : Neurones and temperature regulation. In *Physiological controls and regulations*, J. R Brobeck, edit., in press, Philadelphia, 1965.

(38) Beckman (E. L.) : *Nav. Med. Res. Inst.*, Personal communication.

(39) Thauer (Rudolf) : Der nervöse Mechanismus der chemischen Temperaturregulation des Warmblüters. *Die Naturwissenschaften*, 1964.

(40) Randall (W. C.) et al. : Central and peripheral factors in dynamic thermoregulation. *Journ. of Appl. Physiol.*, 1963, **18**, 61.

(41) Hardy (J. D.) et al. : Observations on the physiological thermostat in homoeotherms with motion picture. *Abstract in Science*, 1962, **136**.

(42) Cooper (K. E.) et al. : Temperature in the external auditory meatus as an index of central temperature change. *Journ. of Appl. Physiol.*, 1964, **19**, 1032.

(43) LAGERWERFF (J. M.) and FYFFE (H. D.) : An electronic ear-thermometer using a new principle in subject monitoring. *Proceedings of the 17th Annual Conference, Engineering in Medicine and Biology*, Cleveland, Ohio, Abstract 6-6, 1964.

(44) WORTZ (E. C.) : Development of a new tech.rique for measuring temperature changes of the tympanic membrane. *Airesearch Manufacturing Division*, Garrett, Los Angeles, 1965.

(45) ADDUCCI (A. J.) et al. : Ovulation detection by internal cranial measurement of temperature. *Bio-Medical Engineering*, 1965, 12, 2.

(46) PIIRONEN (PEKKA) : Effects of exposures to extremely hot environments on temperatures of the tympanic membrane, the œsophagus, and the rectum of men. *Technical documentary Report*, Department of Physiology, Institute of Occupational Health, Helsinki, Finland, 1963.

(47) GUIDRY (A. J.) and McDOWELL (R. E.) : Tympanic membrane temperature for determining the response of cattle to heat stress. *J. Dairy Sci.*, 1965, 48, Abstract 6.

DISCUSSIONS

HARDY. — I would like to ask just one or two questions. As the years go on, Dr. Benzinger, and I found ourselves getting closer together as to the conception of temperature regulation and I was very glad to hear at this morning that Dr. Benzinger feels that the regulation system is a very complex one. I had an idea that some years ago he told it was much more simple. It seems now that the main area of disagreement matters whether the skin temperature does actually drive the system of warm thermo-regulation that is thermo-regulation against heat or not. Dr. Benzinger suggested that we repeat this experiment and we have done a number of them and we find that, in general, his observations were quite accurate. If you put a man on the heat and if you give him an ice-cream to eat, he will indeed stop sweating and his skin temperature will indeed go up. The interpretation of this very interesting but complicated experiment seems to me not as that Dr. Benzinger would have it : that his skin is doing nothing. The skin is trying hard to do anything because there has been other reason by the effects from the internal thermo-receptors for cold which some area seems to have a very much part of play and the thermo-regulations against cold from the first way. The experiments that we have done on thermo-regulation on exposing a man to progressive degrees of warm showed conclusively that the skin does drive the system and quite independent of the tympanic temperature. The only thing that separates Dr. Benzinger and myself now seems to me a few more experiments on Dr. Benzinger's part. The double action of the thermo-regulatory system in dog and cat and man is undoubtedly very confusing. And for that reason, you can get almost any result that you wish depending on how you do your experiments. This means of course that in the specification of the experimental procedure you have to be clear, but also that the interpretations which are made from many experiments have to be very cautions indeed. We can certainly show under certain circumstances that the thermo-receptors are driving the system for heat regulation that is regulation against heating, we can

also show quite the opposite, we can show exactly the opposite experiment of the ice-cream experiment in which the tympanic temperature is going down and the skin temperature is going up and the sweating is going up. There is no problem with any of this if you want to do the experiment in a particular way. And, therefore, I think that Dr. Benzinger and I have moved a step closer now and I have a couple of questions to propose to him, simply to make sure that I've understood his position as up to-day. The first of these questions has to do with the skin temperature drive and I'll like to ask to Dr. Benzinger : Do you still maintain your original position that the skin temperature above 33 degrees do not participate in thermo-regulation against heat ? The second question is that : do you conceive very small changes of temperature in the hypothalamus or near the tympanic membrane when this temperature level is near to neutral are actually necessarily evoking thermo-regulatory responses ? And, thirdly, do you admit that the cooling of the hypothalamus area or of the internal evokes no thermo-regulatory responses to cold ? And I would include man here, because I think man is not terribly different from the goat, or the dog, or the cat.

BENZINGER. — I am very grateful to you, Dr. Hardy, that you put your questions so precisely. I shall try to answer your questions in order : First, does a skin drive exist for sweating and by drive, one would mean warm impulses, arising from receptors of the skin driving the sweating responses ? I would say that all I know makes this unlikely. On the other hand, certainly the activity of sweat glands is not entirely independent of their temperature, of their own temperature. There are factors affecting these activities, circulatory factors and many others. And results have shown that they all have some influence when you divide skin and internal temperature beyond physiological relations. If you warm a certain small area of the skin and keep the rest of body at a different temperature, then the sweating response is not the same from these parts which I think can be reasonably expected. So, my position is that I do not think that there is really a neural warm drive from skin warm receptors to this system of sweating. But there is a decisive influence of skin temperature on vasodilation. Even when you cut all nervous connections to the skin vessels, the vessels will react upon warm and this may indirectly have an affect on sweating, of course. I do believe that there are cold drives from the skin, inhibiting sweating although this is not yet firmly established. This may have been one of the main reasons for difficulties in reconciling results from different laboratories.

Your second question was : Do I believe that any change in hypothalamic temperature near the set-point does necessarily evoke a thermo-regulatory responses ? This is perhaps a matter of time; it takes some time for this response to develop because the reverberating neurone network is very complex. It takes a reasonable time, perhaps a few minutes, but we have not looked for more rapid changes. I would expect such responses to take place and here again it is a difficulty of reconciling your findings in the dog with the changes I observed in man. I do not have the explanation, why the thermo-regulation

of a dog in your experiment was not oscillating in response to the changes which I observed in man.

The third question is a very interesting one : Does man have cold-receptors in the hypothalamus ? I think nothing is known except from experiments in the dog. They appear from the experiments of Dr. Chatonnet and particularly from your own studies where you have shown these neurones. Other authors have shown excessive reactions of central receptors in response to sudden cooling which make them in some way similar to skin thermo-receptors. It has been shown on the other hand but not with the same methods that they seem to be absent in the cat. And if I rememorize well you made the comment that you believed that this is a true absence and not just an incidental omission in observations. So there is perhaps not a qualitative but at last a quantitative difference between different species in this respect. And the explanation would be that cold-receptors in the brain, if they exist in man, they are rudimentary. This is based not only on my experience as I have not been able to observe shivering in man with a warm skin. But Beckman also made observations in hundreds of experiments and he has never observed shivering in man with a warm skin. He put these subjects with low internal temperature under warm showers. They did not shiver. As soon as they leave the warm shower, having still a lower internal temperature, they start shivering violently but they never shivered in his experience with a warm skin. I made on myself some observations on shivering after being undercooled to a very low temperature. In a warm bath I had some slight trembling which rapidly disappeared. So, perhaps, the most likely state of affairs is that man on one time perhaps possessed such cold-receptors and still has some rudiment of them. It makes it very interesting in connection with what has been observed on animals. Does this answer your questions ?

DOCUMENT CONTROL DATA - R & D

Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified

1. ORIGINATING ACTIVITY (Corporate author)	2a. REPORT SECURITY CLASSIFICATION
NAVAL MEDICAL RESEARCH INSTITUTE NATIONAL NAVAL MEDICAL CENTER BETHESDA, MARYLAND 20014	UNCLASSIFIED
	2b. GROUP

3. REPORT TITLE

THE THERMAL HOMEOSTASIS OF MAN

4. DESCRIPTIVE NOTES (Type of report and inclusive dates)

Medical research interim report

5. AUTHOR(S) (First name, middle initial, last name)

BENZINGER, Theodor H

6. REPORT DATE	7a. TOTAL NO. OF PAGES	7b. NO. OF REFS
October 1967	56	47

8a. CONTRACT OR GRANT NO.	9a. ORIGINATOR'S REPORT NUMBER(S)
NASA H R-8 and R-38	
b. PROJECT NO	MR005 01 0001- Report No. 9
c.	9b. OTHER REPORT NO(S) (Any other numbers that may be assigned this report)
d.	

10. DISTRIBUTION STATEMENT

Distribution of this document is unlimited

11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY
Reprinted from Fondation Singer-Polignac, Paris, France, 1967, pp 325-379	Bureau of Medicine and Surgery (Navy) Washington, D. C.

13. ABSTRACT

In further attempts to understand the thermal homeostasis of man new methods - gradient layer calorimetry and cranial thermometry - were developed and utilized. Gradient calorimetry and indirect calorimetry permitted to measure at low inertia, losses or gains of heat, the effects or responses in thermoregulation. Cranial and skin thermometry permitted to measure directly, physical causes or stimuli near the sites of reception. Quantitative, reproducible and physiologically meaningful relations between stimuli and responses were observed. The stimuli are subtle, the responses are powerful by comparison. Physical thermoregulation was found to be elicited by central warm-reception. Chemical thermoregulation was found to originate from cold-reception at the skin. Yet, it is ultimately controlled like physical thermoregulation by central warm-reception, with an inhibitory function.

The findings of gradient calorimetry and indirect calorimetry combined with cranial thermometry are consistent with the classical discoveries on ruling centers and pathways of thermoregulation. They are consistent with the temperature-dependent patterns of firing rates in peripheral or central, cold or warm receptive neurons as observed in other laboratories.

Power and precision, thresholds, ranges and limitations of the autonomic mechanisms were described. A comparison of the calorimetric findings with well-known concepts of engineering demonstrated basic similarities between man and his technical devices. Servsome chanisms and negative feedback, lead-errors and the setpoint, on-off, proportional and rate-control were found to be common to physiological mechanisms in man, and man-made control systems. Applications of the experimental findings and cranial thermometry techniques are briefly discussed.

An investigation of behavioral thermoregulation revealed, that the conscious, sensory information on which the willfull psychomotor responses depend derives from peripheral cold- and central warm-reception, much like is autonomic thermoregulation. Unlike the motor-autonomic response to cold, however, the behavioral response to cold is not subject to central warm-inhibition.

In the broad scope of thermal stress which it may cover, behavioral thermoregulation is superior to autonomic control. Its range isn't matched for most practical purposes, when technology extends the resources of intelligent thermal behavior with external supply of energy. Nevertheless, only the autonomic system can provide the almost incredible precision and reproductibility of the thermal homeostasis of man.

Supreme autonomic control of thermal homeostasis by the nervous system was envisioned by Claude Bernard. His views were substantiated in numerous classical investigations during this first century following his main work. It was our limited task to demonstrate experimentally how homeostatic control is enforced by the central nervous system, as human body temperature is held close to an absolute setpoint by means of a human thermostat, a terminal sensory organ for warm-reception in central position

KEY WORDS	LINK A		LINK B		LINK C	
	ROLE	WT	ROLE	WT	ROLE	WT
Thermal homeostasis						
Gradient layer calorimetry						
Tympanic thermometry						
Physical thermoregulation						
Chemical thermoregulation						
Cold reception at the skin						
Central warm reception						
On-off, proportional and rate control						
Setpoint of thermostat						
Behavioral thermoregulation						
Peripheral cold and central warm reception						
Human thermostat						
Temperature eye						

END